Oncologic Drugs Advisory Committee Meeting Briefing Document

Pixantrone dimaleate (BBR 2778) Injection for the treatment of patients with relapsed or refractory aggressive Non-Hodgkin's Lymphoma who have received 2 or more prior lines of therapy

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EXECUTIVE SUMMARY

Introduction

Cell Therapeutics has submitted an original New Drug Application (NDA) under section 505(b) of the Federal, Food, Drug, and Cosmetic Act for PIXUVRI™ (pixantrone dimaleate) injection, seeking accelerated approval under section subpart H, for the treatment of relapsed or refractory aggressive Non-Hodgkin's Lymphoma (NHL) in patients who have received two or more prior lines of therapy. Pixantrone (also known as BBR 2778) was granted fast track designation by the FDA for this patient population. This NDA is based on the randomized multicenter, international, controlled trial, PIX 301, also known as the EXTEND study (Expanding the reach of anthracyclines with piXanTronE in relapsed or refractory aggressive NHL Disease). A total of 140 patients with aggressive NHL were enrolled in PIX301 over the course of 45 months in the United States, Eastern and Western Europe, Latin America and India.

The pixantrone clinical program in NHL is comprehensive. The safety database includes 348 patients who have been treated with pixantrone, 80% of whom had relapsed or refractory NHL. In addition to the 68 patients treated with single-agent pixantrone in PIX301, 129 patients have received pixantrone as a single agent in other studies, and 151 patients have received pixantrone in combination regimens.

Pixantrone is a novel aza-anthracenedione compound related to anthracyclines and anthracenediones such as doxorubicin and mitoxantrone, classes of drugs whose antineoplastic activity is linked to inhibition of topoisomerase II (TOPO-II) and DNA intercalation. Pixantrone exhibits physiochemical and DNA-binding properties that are distinct from these agents.[1] Pixantrone forms stable DNA adducts through alkylation with specificity for DNA hypermethylated sites.[2.] Importantly, unlike other anthracycline-like agents, pixantrone cannot bind iron and as such does not perpetuate the generation of toxic oxygen-free radicals, the putative mechanism linked to acute cardiac toxicity of other anthracycline-like agents. In addition, pixantrone does not form alcohol metabolites like doxorubinol, which are implicated as an important contributor to late onset cardiac toxicity.

Overview of Relapsed/Refractory Aggressive NHL

Non-Hodgkin's lymphomas (NHL) are the sixth most common type of cancer, with an incidence of 66,000 patients annually in the United States.[3] Aggressive NHL comprises 60% of all NHL, of which diffuse large B-cell lymphoma (DLBCL) is the predominate histologic subtype, accounting for 75% of all aggressive varieties. Unlike with indolent NHL, survival for patients with aggressive NHL, irrespective of histology, is short without intensive chemotherapy or chemoimmunotherapy.[4]

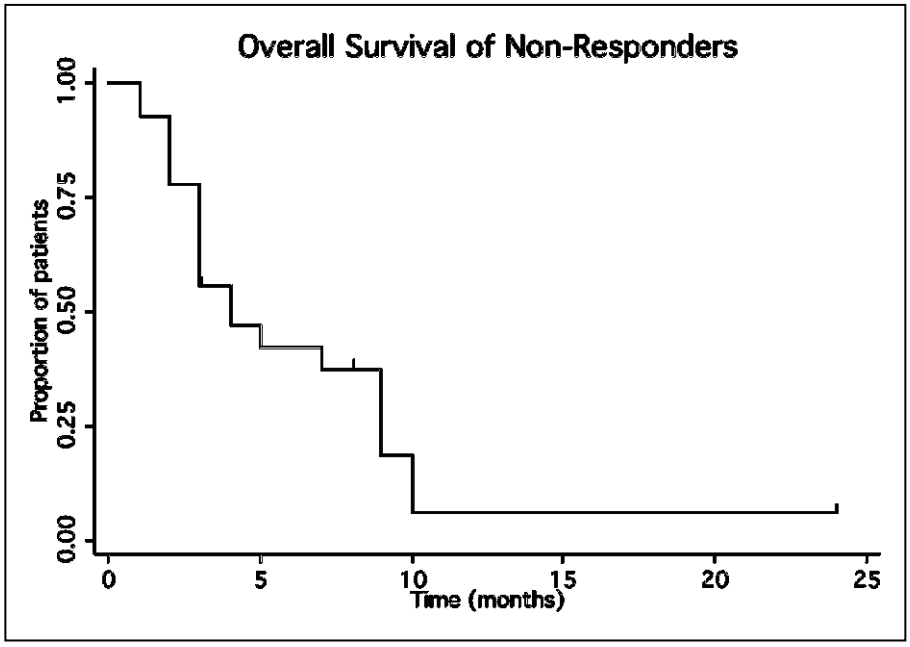
Anthracyclines are the most active class of agents in treating NHL. Front line anthracycline based chemoimmunotherapy can be curative for approximately 50% to 70% of patients with DLBCL. However for patients with less chemosensitive histologic subtypes like T-cell, anaplastic large cell, transformed indolent, or patients who relapse following or who are refractory to front-line therapy, the likelihood of durable remission or cure decreases with subsequent second-line multiagent regimens. Patients who relapse after CHOP-R front-line therapy and receive high-dose myeloablative regimens followed by autologous stem cell transplant (ASCT) have a 3-year disease-free survival of approximately 20% with a median PFS of 6.5 months.[5] For patients who relapse after second-line regimens, the outcome is grim with low response rates, rare complete remissions using existing agents, and overall survival expectations of less than 6 months.

Need for New Treatment Options in Patients with Relapsed or Refractory Aggressive NHL

There is no standard treatment for patients with relapsed/refractory aggressive NHL beyond second-line treatment regimens, irrespective of histologic subtype. The National Comprehensive Cancer Network (NCCN) guidelines recommend investigational agents in clinical trials or palliative therapy for care of such patients. In the US, there are no approved agents in this setting and as such, investigational agents or agents approved in other settings are tried as systemic therapy in these patients including immunotherapy, combination-agent chemotherapy, or single agent chemotherapy. Reports from single institution, uncontrolled trials demonstrate consistently low CR/CRu rates (0% to 13%), short durations of response (2 to 3 months when reported) and short overall survival (< 6 months).[6]

Recent experience from the Cornell Weill Medical Center for patients with DLBCL who fail second-line therapy is shown below.[7]

Figure 1 Survival of Nonresponders to Second-Line Therapy (Cornell-Weill experience)



Elstrom 2009, in press. .

New therapies that can produce meaningful rates of durable complete response, superior disease control rates and a significant prolongation of PFS may ultimately contribute to the development of new regimens that enhance overall survival in patients with relapsed/refractory aggressive NHL.

Efficacy and Safety of Pixantrone in Relapsed/Refractory Aggressive NHL

PIX 301 Study Design

Prior to its initiation, the pivotal study protocol (PIX301, CTI study) was reviewed under the Special Protocol Assessment (SPA) process with the Division of Oncologic Drug Products (DODP). The primary efficacy endpoint suggested by the FDA and agreed to by the sponsor was the complete response (CR) and complete response unconfirmed (CRu) rate in the Intent to Treat (ITT) population as determined by the Independent Assessment Panel (IAP).

The randomized controlled trial included 140 patients with institution-determined aggressive NHL enrolled over 45 months at 66 of 189 study sites in 24 countries. Patients 18 years or older with stage III to IV aggressive NHL who had adequate organ function including left ventricular ejection fraction of 50% or greater were eligible. Patients were required to have received at least 2 prior lines of systemic therapy such as chemotherapy or chemoimmunotherapy which could include ASCT following myeloablative therapy. Randomization was stratified by region, International Prognostic Index (IPI) Score, and prior stem cell therapy. The study Sponsor and independent response assessment panels were blinded to treatment assignment.

Patients were randomized to pixantrone 85 mg/m^2 given by 1 hour infusions on days 1, 8, 15 of each 28-day cycle for up to 6 cycles or to physician's choice of single-agent comparator drug most appropriate for that patient at that comparator agent's standard dose and schedule. Response and disease progression assessments were standardized to every 8 weeks (+/- 1 week) through end of treatment (EOT) and during the18 month post EOT follow-up. Additional information was collected on secondary treatments if utilized following the EOT period. Patients receiving secondary therapies were treated as having a progression event whether or not their disease had progressed.

The primary efficacy endpoint was based on the IAP determined rate of complete response (CR) and unconfirmed complete response (CRu) in the ITT population based on International Working Group criteria (1999).[8] An independent radiologic assessment committee (IRC), blinded to treatment assignment, performed radiographic response evaluation every 8 weeks (+/- 1 week) throughout treatment and during the follow-up period.

An IAP consisting of an independent radiologist, oncologist, and pathologist reviewed all IRC radiographic assessments, including baseline through EOT and follow-up assessments, in conjunction with relevant clinical, biochemical and pathologic information, to determine response. If a majority (2 of 3) of IAP members did not agree on response assessment, the lowest response was assigned. In addition, prespecified supportive efficacy analyses were performed. All analyses conducted were described in the statistical analysis plan and agreed to by FDA during the SPA process.

As prospectively defined in the protocol, pixantrone would be considered active in relapsed/refractory aggressive NHL if in the ITT population the CR/CRu rate in pixantrone recipients was significantly ($p \leq 0.05$) higher than the CR/CRu rate in patients treated with the

physician's choice of comparator agents. Initial statistical power assumptions were based on demonstrating a 10% absolute increase in CR/CRu rate between treatment arms, with 80% power requiring a sample size of 320 patients. The Data Monitoring Committee (DMC) conducted a futility analysis in a closed session independent of the Sponsor after 40 evaluable patients were enrolled and recommended that the study continue.

Enrollment in PIX301 was slow, and despite several measures aimed at enhancing accrual (widening inclusion criteria, opening 100 additional sites in 15 additional countries) a decision was made, following discussion with the FDA, to close enrollment after the 140th patient was randomized, 45 months from the start of the study. The planned interim analysis was cancelled; only one analysis was conducted per the original statistical analysis plan. The Sponsor remained blinded to treatment assignment until database lock in February 2009.

The primary efficacy results were determined by the IAP in the ITT population. Prospectively-defined secondary endpoints included overall response rates (ORR), response lasting ≥ 4 months, duration of CR/CRu, PFS, overall survival (OS) and safety. Two additional sets of prespecified supportive analyses were conducted on the efficacy endpoints (CR/CRu, ORR, PFS) to examine the robustness of the results. These included investigator assessment of response as well as applying the IAP response assessments to a retrospective independent central review of histology, referred to as the HITT population.

Exploratory analyses examining potential effects of age, IPI, geography, prior stem cell transplant, performance status, prior anthracycline exposure, and prior rituximab exposure on CR/CRu and PFS were also conducted.

Standard safety evaluations were conducted to monitor adverse events. In addition, given the relationship of pixantrone to anthracycline like agents, comprehensive evaluation of cardiac function was prospectively incorporated into the study design with specific cardiac adverse event reporting requirements by the investigator whether or not such adverse events were deemed related to study drug. Assessment of cardiac left ventricular ejection fraction (LVEF) as determined by echocardiogram or MUGA at baseline then every 2 cycles and at 6 months following EOT was also prospectively incorporated into the study design. NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3 was utilized to evaluate safety.

Baseline Demographics and Characteristics of the Relapsed/Refractory Aggressive NHL Population

The patient population treated in PIX301 is representative of US histologic subtypes and treatment practices.[9] Seventy-five percent (75%) of patients were classified as DLBCL by the investigator's institution, 14% as transformed indolent, 7% as peripheral T-cell, and 4% as anaplastic large cell or follicular grade III. While intended to be a third-line treatment study, approximately 58% of all patients had received three prior lines of therapy and 15% had received and failed prior myeloablative therapy and SCT. Over 70% of patients had Ann Arbor stage III/IV disease, with 57% being refractory to their last line of therapy.

The most common front-line therapy was standard anthracycline based CHOP+/-rituximab like regimens in 93% and 90% of pixantrone and comparator patients, respectively. Rituximab use was consistent with then accepted treatment practices during the 45-month period (2004 to 2008) for study enrollment. Sixty-five of 105 patients (62%) with DLBCL had received 1 or more rituximab-containing regimens at some point over their first, second or third-line therapy prior to entering PIX301.

Second and third-line regimens utilized prior to PIX301 randomization in patients who relapsed after first-line therapy were also representative of those commonly applied in the United States, including etoposide, ifosfamide, platinum and high-dose cytarabine based regimens (ESHAP+/-R, DHAP+/-R, ICE+/-R, BEAM+/-R, GemOx+/-R, radioimmunotherapy, CNOP+/-R).

Treatment arms were well balanced across geography, histology, Ann Arbor Stage, IPI score, number of prior chemotherapy regimens, response to most recent chemotherapy, SCT, and relapsed or refractory status.

Primary Efficacy Findings

PIX301 successfully met the primary efficacy endpoint of the study (Table 1). Twenty-percent of pixantrone recipients achieved a CR/CRu compared to only 5.7% of patients treated with comparator agents (p=0.021). No patients (0%) in the comparator arm achieved a confirmed complete response compared to 8 patients (11%) of pixantrone recipients.

Table 1 Primary Efficacy Endpoint: Patients with CR or CRu by IAP Assessment (ITT Population)

Data Cutoff 30 Sep 2008

	Pixantrone (N=70)	**Comparator (N=70)**	***P*-value**
CR/CRu, n (%)	14 (20.0%)	4 (5.7%)	*0.021*
95% CI	(11.4%, 31.3%)	95% CI (1.6%, 14.0%)	
CR, n (%)	8 (11.4%)	0 (0%)	
95% CI	(5.1%, 21.3%)	95% CI (0%, 5.1%)	
CRu, n (%)	6 (8.6%)	4 (5. 7%)	
95% CI	(3.2%, 17.7%)	95% CI (1.6%, 14.0%)	

Source: PIX301 CSR Table 14.2.1
Fisher exact test was used to compare proportions in the pixantrone and comparator groups.

The overall response rate (ORR) was also significantly higher among pixantrone recipients (37% vs 14%, p=0.003). Responses (ORR and CR/CRu) with pixantrone were more durable than responses in comparator patients, with 26% of pixantrone responses (CR, CRu, PR) lasting ≥ 4 months compared to only 9% of comparator responders (p=0.012). Median duration of CR/CRu was also longer (7.0 months vs 3.4 months, HR 0.25, p=0.033) as of 30 Sept 2008 data cutoff (Figure 2). Figure 3 shows duration of CR/CRu by individual patients.

Figure 2 Duration of CR/CRu by IAP (ITT Population)

Data Cutoff 30 Sep 2008

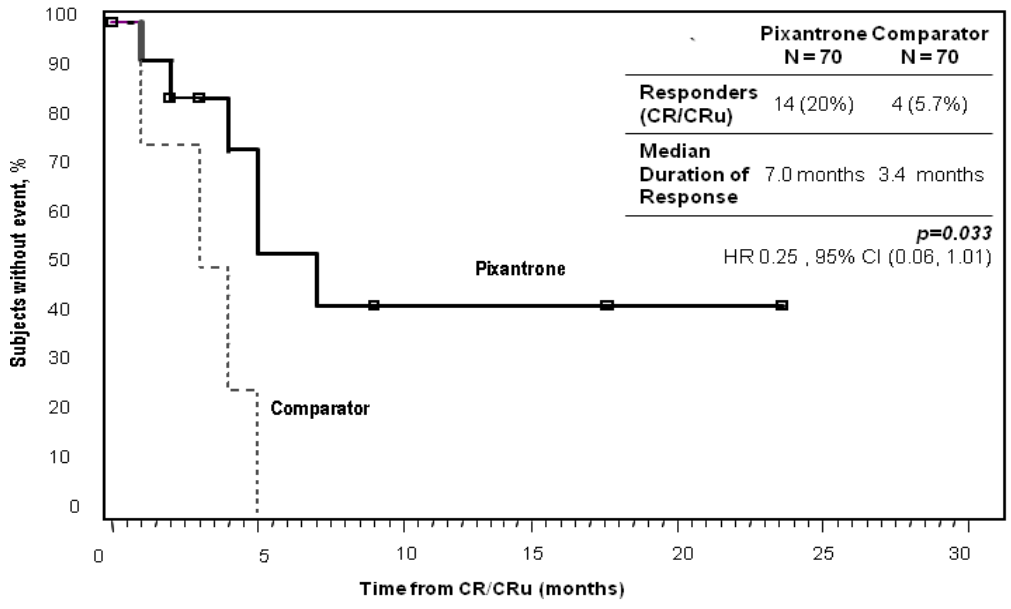


Figure 3 Duration of CR/CRu by Patient IAP Assessment (ITT Population)

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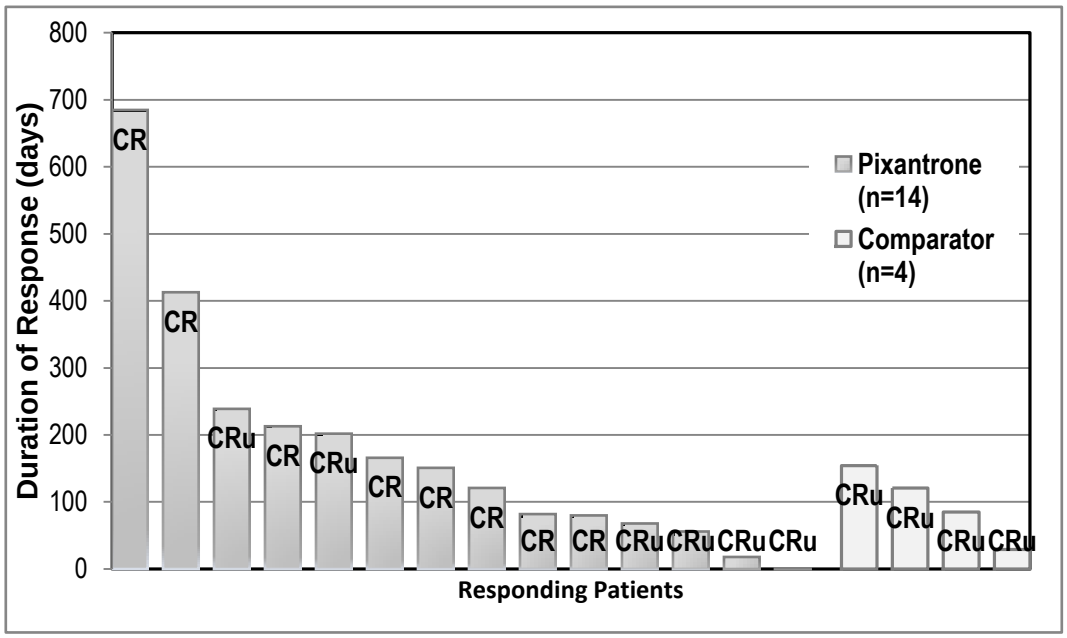

The higher response rate to pixantrone was associated with a highly significant 40% increase in PFS (4.7 vs 2.6 months HR:0.60, p=0.007) (Figure 4).

Figure 4 PFS by IAP Assessment (ITT population)

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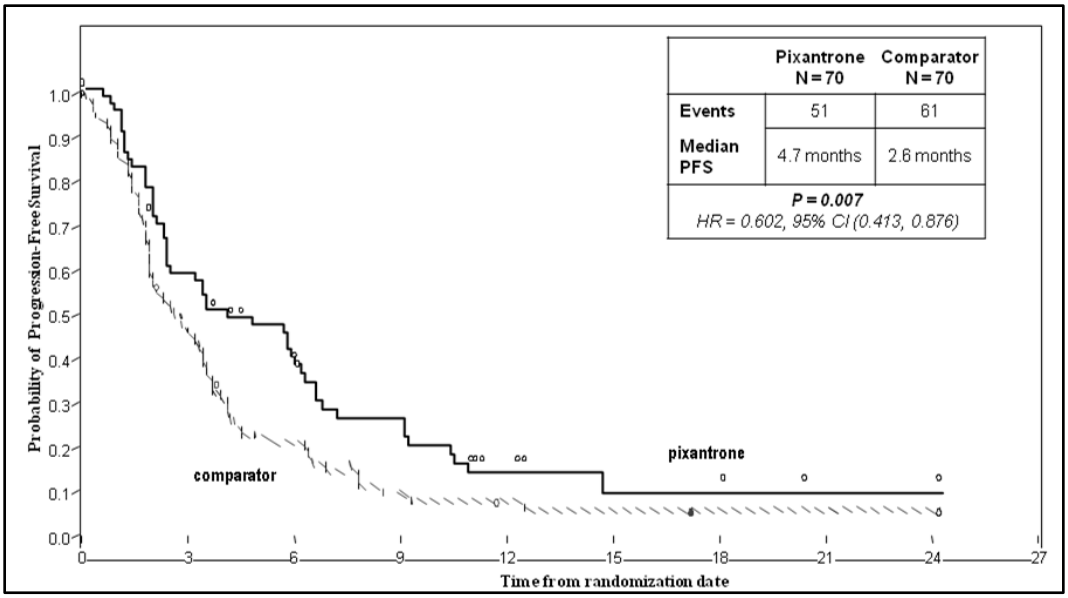

While PIX301 was not powered to demonstrate an effect on overall survival, with 85 reported deaths a nonsignificant 12% reduction in the rate of death and a 1.2 month increase in overall survival was observed. The primary efficacy results demonstrate that pixantrone was significantly more effective than currently available single-agent treatment of patients with relapsed or refractory aggressive NHL who have received two or more prior lines of therapy.

Prespecified Supportive Analyses

While the primary efficacy results were determined by the IAP in the ITT population, two additional sets of analyses were conducted on the efficacy endpoints (CR/CRu, ORR, PFS) to examine the robustness of the results. These prespecified analyses included investigator assessment of response as well as applying the IAP response assessments to a retrospective independent central review of histology, referred to as the HITT population.

Figure 5, Figure 6, and Figure 7 respectively, show the point estimates with 95% confidence intervals for CR/CRu, ORR and PFS on the ITT population by IAP assessment, by investigator assessment and by independent central histologic review of IAP determined response.

Figure 5 Comparison of CR/CRu Rates

Data Cutoff 30 Sep 2008

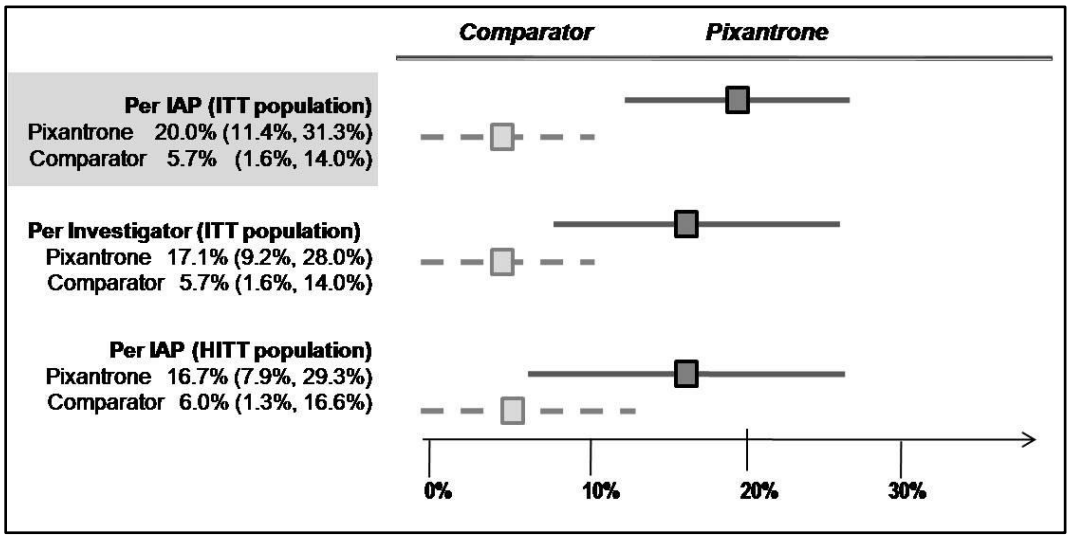

Figure 6 Comparison of ORR

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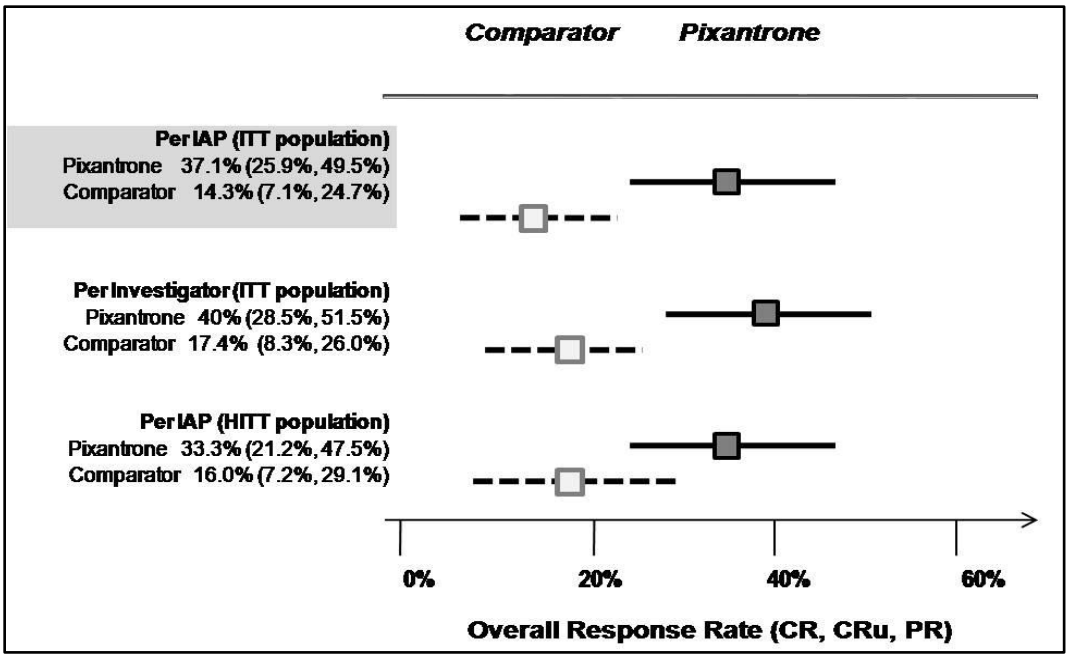

Figure 7 PFS Hazard Ratios and 95% Confidence Intervals

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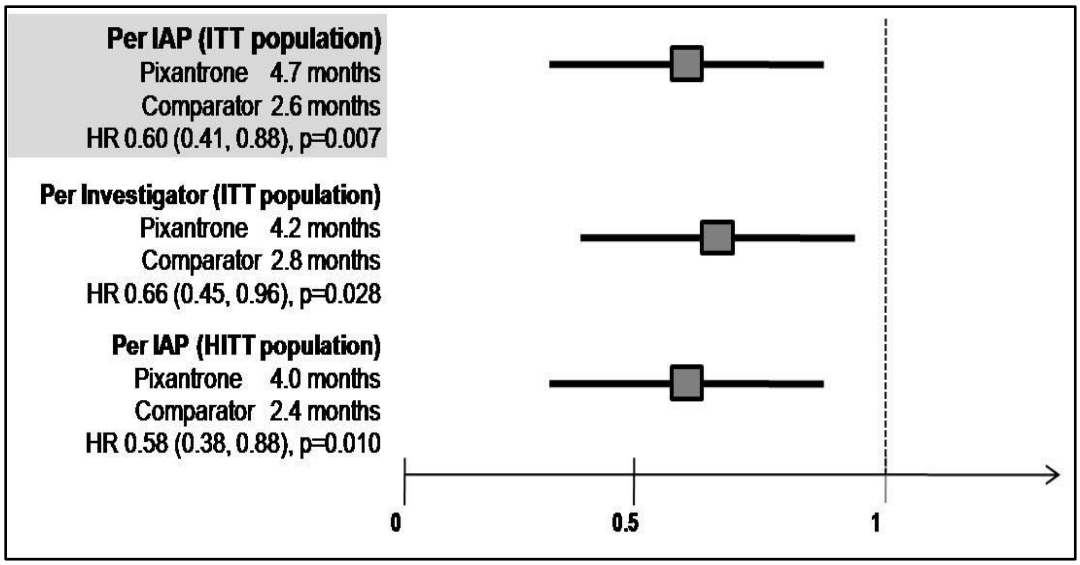
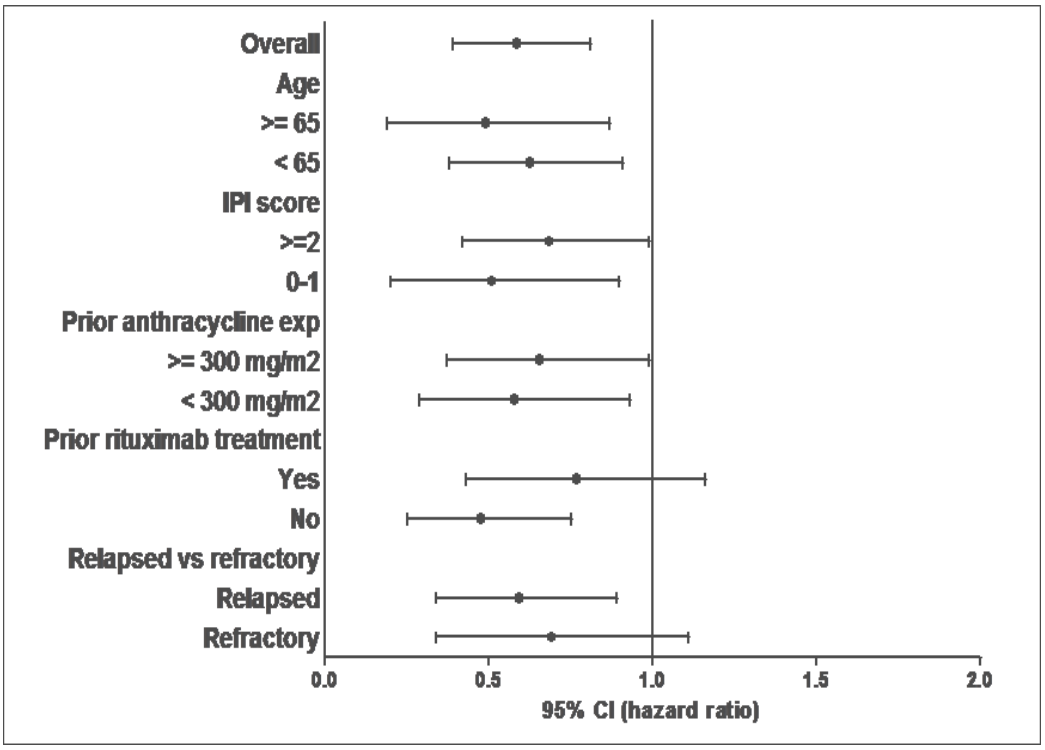


The results underscore the consistency and robustness of the primary efficacy findings across investigator-determined and independent central retrospective histologic assessments. In addition, overall survival (data cutoff 30 September 2008) was consistent between the ITT and HITT populations (HR 0.88 vs HR 0.82, respectively).

Planned Subgroup Analyses of PFS by Prior Therapy or Risk Factors

Forest plots (median +/- 95% confidence interval bands) were constructed to determine the potential impact of prior therapy (rituximab, SCT, prior anthracycline exposure above/below 300 mg/m^2) and disease risk factors on PFS. As shown in Figure 8, PFS consistently favored pixantrone over comparator agents, adding support to the robustness of the primary efficacy findings.

Figure 8 PIX301 PFS Exploratory Analysis



120-Day Post NDA Submission Safety and Efficacy Follow-up Analyses

Additional response and disease progression data were retrieved for submission as part of a required day-120 post NDA safety update. As of the 25 June 2009 cutoff date, all patients still on study had at least 9 months of follow-up. The IAP remained blinded to patient treatment assignment while performing response assessments during follow-up. These assessments further support pixantrone effectiveness; without subsequent therapy, 3 additional patients on pixantrone converted to a CR versus 1 patient on the comparator arm who converted to a CRu. Two additional patients on pixantrone converted to a PR. The updated CR/CRu rate between arms is shown in Table 2.

Table 2 Patients with CR/CRu by IAP (ITT Population)

Data Cutoff 25 Jun 2009

	Pixantrone (N=70)	**Comparator (N=70)**	**P-value**
CR/CRu, n (%)	17 (24.3%)	5 (7.1%)	*0.005*
95% CI	(15.1%, 36.5%)	(2.4%, 15.9%)	
CR, n (%)	11 (15.7%)	0 (0.0%)	*< 0.001*
95% CI	(8.2%, 26.7%)	(0.0%, 5.1%)	
CRu, n (%)	6 (8.6%)	5 (7.1%)	*0.764*
95% CI	(3.3%, 18.0%)	(2.4%, 15.9%)	

Source: 120-Day Report Table 3.1.1
Not included here is pt #081 who received CVP after EOT and converted to a CRu with CRu.
P-value by Fisher exact test.

The overall CR/CRu rate at follow-up was 24% for pixantrone recipients versus 7% for comparator agents (p=0.005) with no (0%) comparator recipient achieving a confirmed CR compared with 11 (16%) of pixantrone patients (p<0.001). As shown in Figure 9, CR/CRu's in pixantrone recipients were more durable, as well as more frequent, than those achieved with comparator agents.

As shown in Figure 10, PFS for patients treated with pixantrone continued to improve with additional follow-up (5.6 vs 2.6 months, HR=0.56, p=0.002) with a 44% reduction in the overall rate of disease progression.

Figure 9: Duration of CR/CRu by Patient (ITT population)

Data Cutoff 25 June 2009

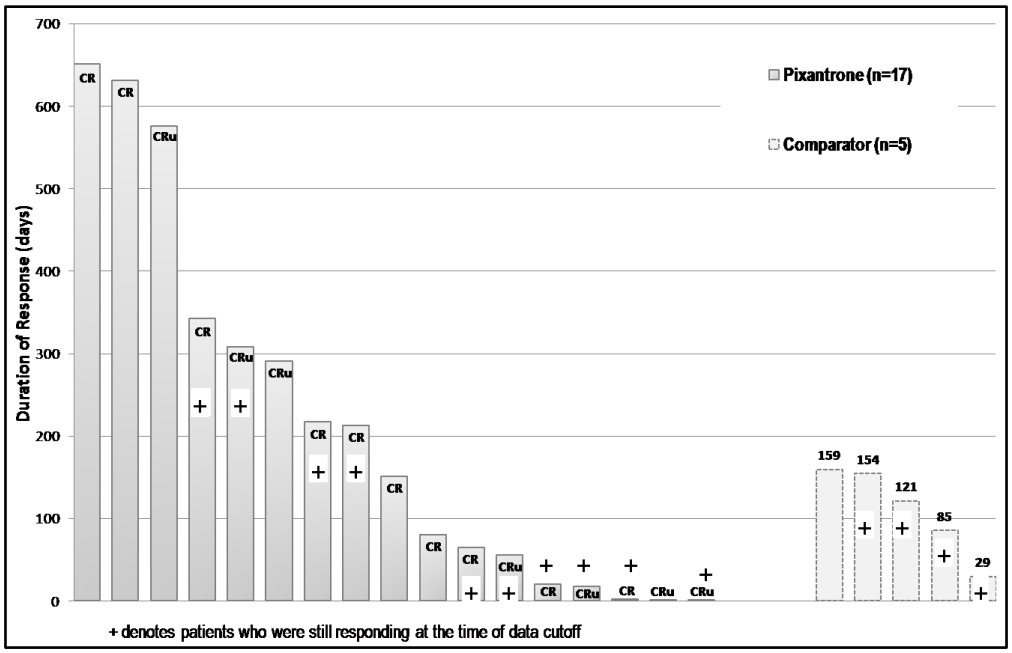


Figure 10: Kaplan Meier Curve of PFS by IAP (ITT Population)

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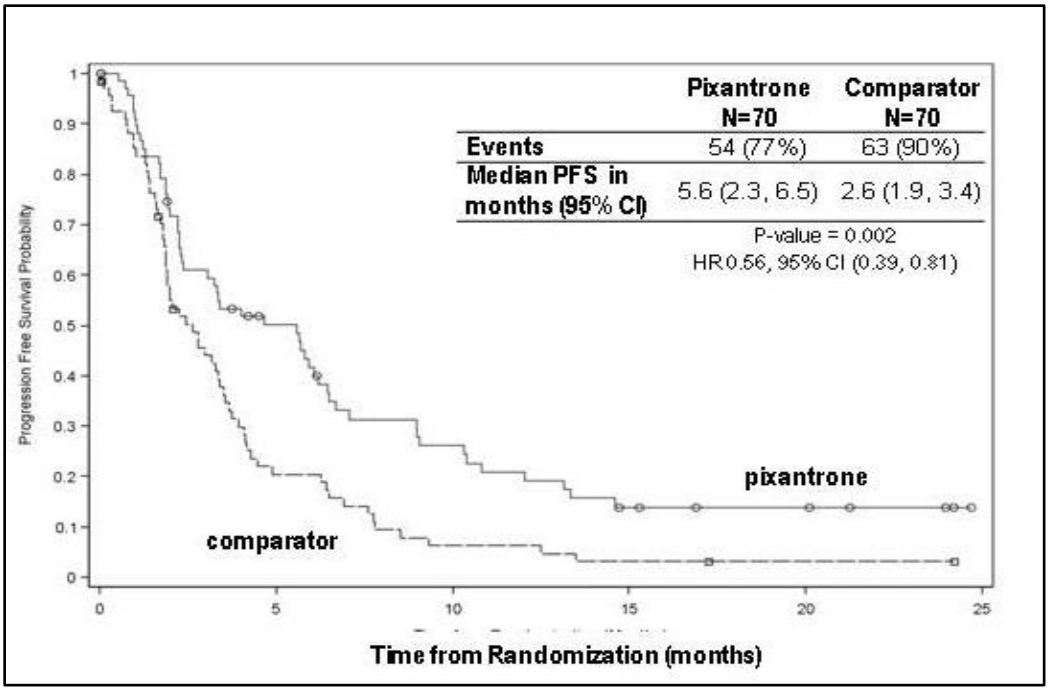
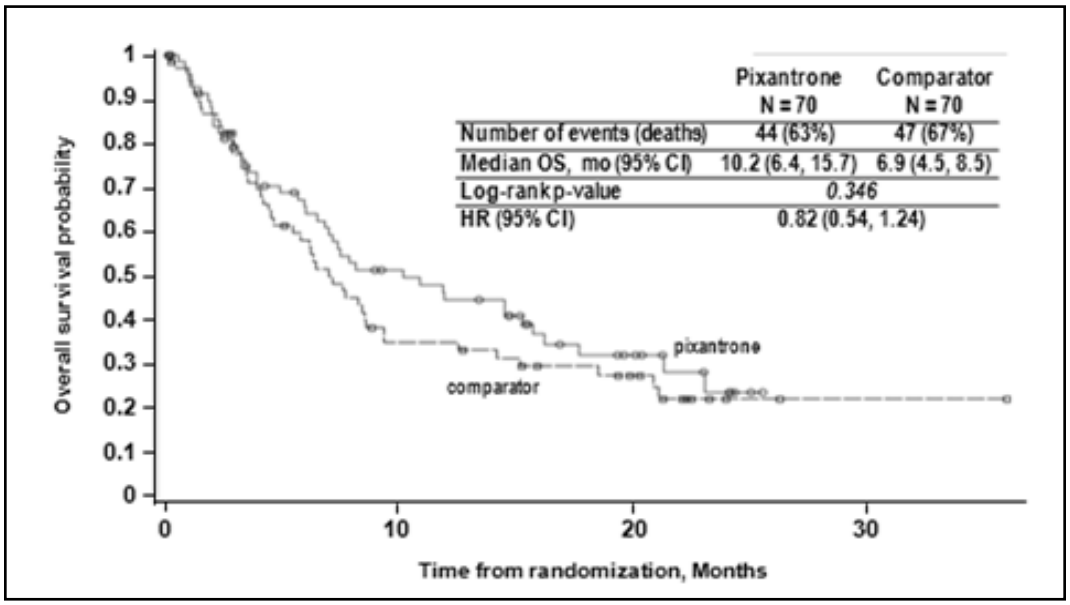


With follow-up of up to 24+ months from randomization, there have been 44 deaths on the pixantrone arm compared with 47 deaths on the comparator arm, and median OS is 10.2 months for patients treated with pixantrone versus 6.9 months for patients randomized to comparator agents (HR 0.82, p=0.346) (Figure 11).

Figure 11 Kaplan-Meier Curve of Overall Survival by IAP (ITT Population)

Data Cutoff 25 June 2009



Primary Safety Findings

The safety profile for pixantrone has been evaluated in a total of 348 patients with hematologic and solid tumor malignancies in both single-agent and multiagent combination regimens. The safety of pixantrone in NHL has been well characterized, as evidenced by exposure in 278 patients with NHL,127 of whom were treated with single-agent pixantrone therapy. These data demonstrate that treatment with pixantrone is associated with manageable side effects. The safety profile is characterized primarily by hematologic toxicities (neutropenia, leukopenia). Nausea, vomiting and alopecia were infrequent following pixantrone administration. Unlike existing anthracycline-like agents, pixantrone is not a vesicant and as such a central line is not required for administration.

The most common (≥ 5% of patients) grade 3/4 adverse events reported in PIX 301 are displayed in Table 18 in section 4.3.1.

While grade 3-4 neutropenia occurred more frequently among pixantrone recipients it was uncomplicated, noncumulative over each subsequent cycle of therapy and associated with a low incidence of febrile neutropenia or infection. Importantly, growth factor support was not routinely required and transfusions with red blood cells and platelets were uncommon.

Pixantrone was well tolerated, with 32% of patients completing all 6 cycles of pixantrone therapy vs 28% of comparator recipients. A median of 4 cycles of therapy was delivered to pixantrone patients compared to a median of 3 among patients randomized to comparator agent. Dose reductions were infrequent in both arms; 12 patients (18%) on the pixantrone arm compared with 10 patients (15%) on the comparator arm required a dose reduction. Discontinuation of therapy for AEs was more frequent among pixantrone patients (21% vs 13%). Relative median dose intensity was 91% for pixantrone recipients.

Since LVEF declines and clinical congestive heart failure (CHF) have been associated with cumulative doxorubicin (anthracycline) equivalent exposure, comprehensive cardiac function evaluation and heightened investigator requirements for reporting potential events, irrespective of relationship to study drug, were an important feature of the PIX301 study. The relationship between severe LVEF declines (≥ 20% from baseline), and clinical CHF (gallop cardiac rhythm, elevated central venous pressure, pulmonary rales, low O_2 saturation etc) is well established for doxorubicin, with clinical CHF rates ranging from 5% at 300 mg/m^2 of cumulative exposure to 26% at 550 mg/m^2 to as high as 48% at exposure levels at or in excess of 650 mg/m^2[10].

In PIX301, a grade 3 LVEF decline occurred in only 1 patient (2%) on the pixantrone arm. Cardiac failure ≥ grade 3 (MedDRA terms cardiac failure and cardiac failure congestive) was reported in 4 pixantrone patients (6%) compared to 1 patient (2%) among comparator recipients. All but one LVEF declines were grade 1/2, with a median LVEF decline of 5 percentage points from baseline to EOT on the pixantrone arm compared to 1 percentage point increase on the comparator arm.

The median pre-PIX301 doxorubicin equivalent exposure was 292 mg/m^2 for pixantrone patients and 312 mg/m^2 for patients on the comparator arm. Following pixantrone therapy the median doxorubicin-equivalent cumulative exposure was (527.9 vs 330.8 mg/m^2; *P* <0.001, range 400 mg/m^2 to > 900 mg/m^2). Unlike doxorubicin, pixantrone was not associated with a cumulative dose-dependent increase in clinical CHF or declines in LVEF despite 34 of 68 patients (50%) who received pixantrone exceeding 550 mg/m^2 of lifetime cumulative doxorubicin-equivalent

exposure by the end of study therapy. The four reported cases of cardiac failure (MedDRA terms cardiac failure and cardiac failure congestive) ≥ grade 3 on the pixantrone arm occurred at cumulative doses at or below 550 mg/m^2.

Deaths within 30 days of last study drug dose were comparable between treatment arms (10 on the pixantrone arm vs 12 on the comparator arm). Adverse events leading to death included disease progression for 4 pixantrone patients and 10 comparator recipients, and pneumonia/sepsis/respiratory failure for 4 pixantrone patients and 2 comparator patients. One patient in the pixantrone group had a pulmonary embolus and another had cardiac failure.

The safety profile noted in PIX301 is consistent across the entire safety database, except for the expected additional hematologic toxicities associated with known contributing side-effects of the other agents utilized in multidrug regimen trials. Cardiac failure (MedDRA terms cardiac failure and cardiac failure congestive) events ≥ grade 3 reported across the entire safety database are similar to that observed in PIX301, occurring in 6 of 197 patients (3%) receiving pixantrone as single-agent therapy and in 4 of 151 patients (3%) receiving pixantrone in combination regimens, despite the majority of patients having received extensive prior doxorubicin equivalent exposure.

Benefit-Risk Evaluation of Pixantrone

In conclusion, pixantrone offers an important therapeutic option for the treatment of patients with relapsed or refractory aggressive NHL who have received two or more prior lines of therapy. The efficacy of pixantrone has been established based on the first randomized controlled trial to demonstrate a clinically meaningful and statistically significant increase in durable complete responses, overall objective responses and progression free survival compared to currently available single-agent therapies. Using independent response assessments, superiority over comparator agents was demonstrated for pixantrone by response rates (CR/CRu, ORR) and PFS and was minimally influenced by disease parameters, prior anthracycline exposure, and prior therapies, including rituximab. There was a 44% improvement in PFS for patients who received pixantrone, and with 91 deaths currently reported, there is an 18% reduction in the death rate for patients randomized to pixantrone compared to patients treated with comparator agents. These results were consistent with prespecified supportive analyses using investigators' institutional assessments of response, as well as IAP response applied to retrospective independent histology review.

With 348 patients in the total safety database, the most common toxicity is reversible, noncumulative and uncomplicated neutropenia.

Unlike existing anthracycline-like drugs, pixantrone does not exhibit a cumulative exposure related increase in grade 3 cardiac toxicity. Despite the extensive prior cumulative anthracycline exposure in most patients, serious cardiac failure (MedDRA terms cardiac failure and cardiac failure congestive) was reported in 10 of 348 patients (3%) during treatment with pixantrone in single-agent or combination studies; 4 of these events resulted in death (1%). Based on data from PIX301, pixantrone is the first anthracycline-like agent with demonstrated significant single-agent activity compared to existing therapies that can be used in patients who have previously been exposed to near lifetime limits of other drugs in the anthracycline class. This allows reintroduction of the most efficacious class of agent in patients with aggressive NHL who have relapsed two or more times.

Overall, pixantrone was well-tolerated with manageable toxicities. With its demonstrated clinical benefit over existing therapies and favorable benefit-risk ratio, pixantrone fulfills an unmet medical need in multiply relapsed patients with aggressive NHL.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABMT	autologous bone marrow transplant
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BBR 2778	pixantrone dimaleate
BSA	body surface area
CAD	coronary artery disease
CHF	congestive heart failure
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CLL	chronic lymphocytic leukemia
CNOP	cyclophosphamide, mitoxantrone, vincristine, and prednisone
CPOP	cyclophosphamide, pixantrone, vincristine, and prednisone
CR	complete response
CRO	Contract Research Organization
CRu	complete response unconfirmed
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
CVP	cyclophosphamide, vincristine and prednisone
CYP450	cytochrome P450
DHAP	dexamethasone, cytaraine, cisplatin
DLBCL	diffuse large B-cell lymphoma
DNA	deoxyribonucleic acid
DODP	Division of Oncology Drug Products
ECG	electrocardiogram
ESHAP	etoposide, methyprednisolone, high-dose cytarabine (ara-C), and cisplatin
EXTEND	Expanding the reach of anthracyclines with piXanTronE in relapsed or refractory aggressive NHL Disease (alternative study name used for PIX301)
FDA	Food and Drug Administration
GemOX	gemcitabine and oxaliplatin
GI	gastrointestinal
HBV	hepatitis B virus
HCV	hepatitis C virus
HDC	high-dose chemotherapy
HITT	histologically-confirmed intent-to-treat
HTN	hypertension
IAP	Independent Assessment Panel

ICE	ifosfamide, carboplatin, and etoposide
IPI	International Prognostic Index
IST	investigator-sponsored trial
ITT	intent-to-treat
LTS	long-term survival
LVEF	left ventricular ejection fraction
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MTD	maximum tolerated dose
MUGA	Multiple Gated Acquisition scan
NCCN	National Comprehensive Cancer Network®
NCI	National Cancer Institute
NDA	New Drug Application
NHL	non-Hodgkin's lymphoma
ns	not significant
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PK	pharmacokinetics
PR	partial response
R-DHAP	rituximab plus dexamethasone, cytaraine, cisplatin
REAL	Revised European-American Lymphoma
R-ICE	rituximab plus ifosfamide, carboplatin, etoposide
SAE	serious adverse event
SCT	stem cell transplantation
sd	standard deviation
SD	stable disease
SPA	Special Protocol Assessment
TOPOII	topoisomerase II
USA	United States of America
WHO	World Health Organization

1 INTRODUCTION

1.1 Proposed Indication and Treatment Regimen

Pixantrone is indicated as a single-agent treatment for patients with relapsed or refractory aggressive non-Hodgkin's lymphoma who have received two or more prior lines of therapy. Pixantrone is to be administered at 85 mg/m^2 by intravenous (IV) infusion on days 1, 8, and 15 of 28-day cycles for up to 6 cycles.

1.2 Background on Aggressive Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphomas (NHL) are a heterogeneous group of diseases originating in various cells within the lymphoid system. Based on pathologic appearance, epitope expression, and clinical presentation, NHL is divided into broad categories of aggressive or indolent lymphoma, and these subtypes can be further classified by cell of origin (B or T cell) and subdivided by pathologic appearance, such as follicular or diffuse. According to the Revised European-American Lymphoma/World Health Organization (REAL/WHO) classification system for lymphoid neoplasms, aggressive lymphomas include:

- diffuse large B-cell lymphoma (DLBCL)
- follicular lymphoma – Grade III
- transformed indolent lymphoma (areas of follicularity allowed)
- mediastinal large B-cell lymphoma
- primary effusion lymphoma (includes previously called immunoblastic lymphoma)
- peripheral T-cell lymphoma, not otherwise characterized
- anaplastic large cell lymphoma
- T/null cell, primary systemic type

Patients undergo staging to define prognosis and appropriate therapy. The staging system most often used in adults is called the Ann Arbor staging system, which uses Roman numerals I through IV.[11] This has been further refined through use of the International Prognostic Index (IPI), which not only includes the Ann Arbor stage, but also includes the number of extranodal sites, age, performance status, and LDH levels (International NHL Prognostic Factors Project 1993). IPI scores ≥ 2 predict a worse prognosis than scores of 0-1, and scores ≥ 3 predict a poor outcome even with standard-of-care therapy.

Approximately 66,120 men and women in the United States were diagnosed with NHL in 2008, with approximately 60% falling into the category of aggressive NHL. More than 19,000 died of the disease in 2008.

1.3 Current Management of Aggressive Non-Hodgkin's Lymphoma

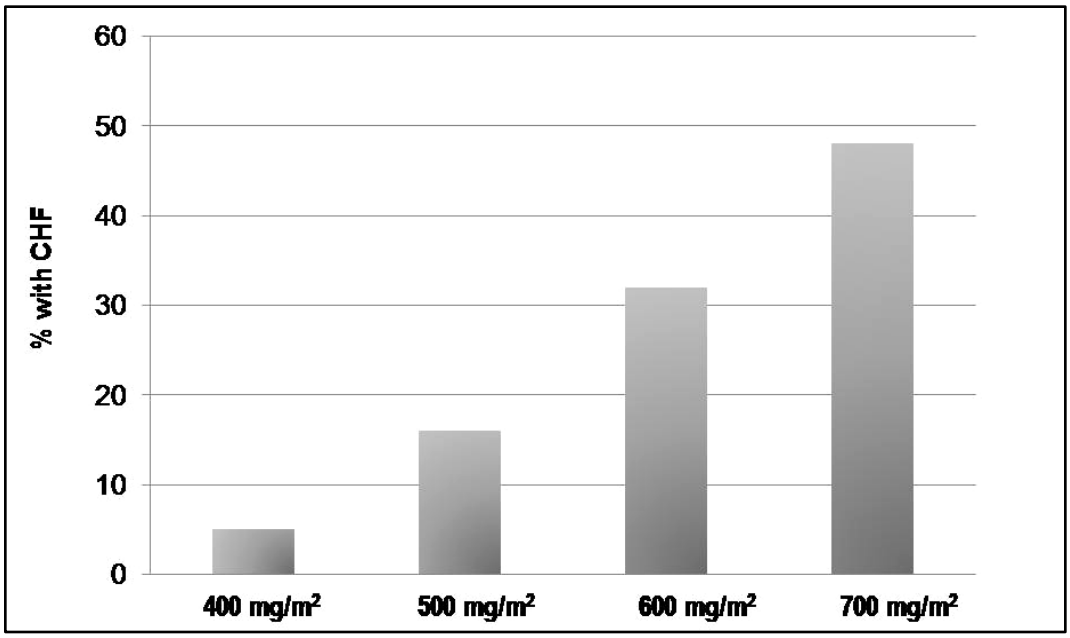
Anthracycline-based regimens have been for many years the standard of care for the initial therapy of aggressive NHL, with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) ultimately becoming the international standard due to its efficacy combined with better tolerability in comparison to other anthracycline-based regimens.[12] CHOP was the international standard of care until 2006 in the USA and 2007 in Western Europe, when CHOP-R (cyclophosphamide, vincristine, prednisone, and doxorubicin + rituximab) became the standard front-line chemotherapy for DLBCL (the most common subtype of aggressive NHL).[13] While a substantial number of patients with aggressive NHL obtain a durable response with initial anthracycline-containing regimens, between 30 and 50% will relapse or prove refractory to initial therapy.

There is no consensus regarding the best regimen for aggressive NHL beyond first relapse in patients not eligible for stem cell transplant or in disease refractory to second-line therapy, and no single agent or regimen is approved or considered standard of care in this setting (NCCN 2009).

Anthracyclines such as doxorubicin are one of the most active drug classes in NHL. However, the majority of regimens utilized beyond the front-line treatment setting do not incorporate an anthracycline or anthracenedione because of the risk for cardiac toxicity associated with an increasing cumulative lifetime anthracycline dose. By the time of first relapse, most patients have received 300 to 400 mg/m^2 of doxorubicin-equivalent cumulative dose, and thus are already near the recommended lifetime limit of 450 mg/m^2 (400 mg/m^2 doxorubicin-equivalent limit if cyclophosphamide or thoracic radiation was previously given) (Doxorubicin Prescribing Information). The amount of additional anthracycline treatment that can safely be used in these patients is therefore limited and these agents are infrequently utilized beyond the front-line treatment setting.

Figure 12 illustrates the increasing incidence of doxorubicin-related CHF versus cumulative doxorubicin dose in patients with breast or small cell lung cancer enrolled in randomized trials of doxorubicin alone or in combination with a cardioprotective agent (dexrazoxane).[14] At cumulative doses of doxorubicin ≥ 550 mg/m^2, the incidence of grade 3/4 CHF reached 26%.

Figure 12 Estimated Cumulative Percentage of Patients with On-Study or Off-Study Doxorubicin-Related CHF by Cumulative Dose (N=630)



Source: Swain,Cancer 2003

In the second-line setting, active nonanthracycline-drugs are most often used, typically in combination with such agents as platinates, cytarabine, ifosfamide, dexamethasone, and etoposide, possibly with additional rituximab. Thus, relatively few additional active agents are available for patients relapsing after second-line salvage therapy.

To date, no randomized controlled trial in NHL patients at or beyond second relapse has been reported. Clinical trials utilizing novel and traditional single-agent therapies (cytotoxic or targeted) in relapsed NHL therapy are limited by small sample sizes, nonrandomized designs, and mixed patient populations that often included mantle cell lymphomas, as well as patients with a better prognosis such as first-relapse elderly patients.

Response rates reported in these studies are disappointing (Table 3), with relatively few confirmed durable complete responses. Additionally, most studies report response rates and duration of response, but not PFS or OS, making it difficult to assess overall clinical benefit.

Despite being the most active class of cytotoxic agents in the treatment of aggressive NHL, anthracyclines other than pixantrone have had limited evaluation in relapsed or refractory NHL beyond the second-line setting.

Table 3 Uncontrolled Single-Agent Trials in NHL

Regimen	Tumor type	# of Patients	Median prior treatments	CR/Cru rate, %	Reference
Bendamustine[1,2]	r/r aNHL	21	2	14%	Weidmann 2002
Bortezomib[2]	r/r NHL	60	3.5	13%	Goy 2005
Oxaliplatin[1,2]	r/r aNHL	23	2	9%	Oki 2005
Rituximab[1]	r/r aNHL	54	1-2[3]	9%	Coiffier 1998
Lenalidomide	r/r DLCBL	49	3	4%	Wiernik 2008
Gemcitabine[1]	r/r aNHL	31	2	0%	Fossa 1999

Abbreviations: r/r = relapsed or refractory; aNHL = aggressive non-Hodgkin's lymphoma
[1]Rituximab naïve
[2] Includes low-grade lymphomas

A study of bendamustine 120 mg/m^2 x 2 days in 21-day cycles in a similar population of 21 patients reported 3 CRs (14%) and 5 PRs, 4 of which were ≤ 3 months in duration.[15] Single-agent oxaliplatin (130 mg/m^2 every 21 days) was also studied in a nonrandomized phase 2 study in 31 NHL patients (23 with aggressive NHL and 8 with indolent) who had failed up to 3 prior regimens[16]; the overall response rate was 27%, with no confirmed CRs and 2 unconfirmed CRs (9%).

Treatment with two dosing regimens of single-agent rituximab was evaluated in 54 rituximab-naïve patients with relapsing or refractory aggressive lymphoma[17]; of the 5 total CRs (9%) reported in the study, all occurred in patients in their first or second relapse. Another study[18] investigating weekly gemcitabine (1250 mg/m^2) for 3 weeks on a 28-day cycle in 31 patients with aggressive NHL who had failed first-line (n=9), second-line (n=11) or third-line treatment (n=11) showed an overall response rate of 19% with no patient (0%) achieving a complete response despite the patient population consisting of almost 30% first-relapse patients.

Thus, there is an unmet need for effective therapy in patients with relapsed or refractory aggressive NHL who have received two or more prior lines of therapy. A drug in the anthracycline class that could be given to patients who had previously received a full course

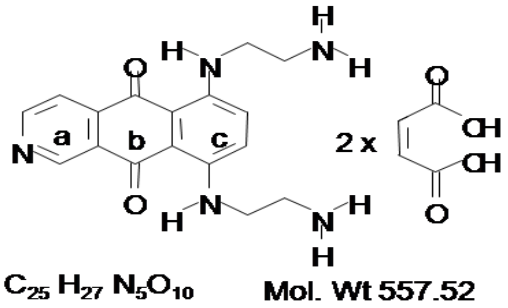
of initial therapy with doxorubicin would be of great value in this patient population. As such, an active agent with manageable toxicities remains an important unmet medical need and could ultimately pave the way for new regimens aimed at improving overall survival in this patient population.

2 PIXANTRONE NONCLINICAL OVERVIEW

2.1 Physical Properties

Pixantrone dimaleate for intravenous injection is supplied as a preservative-free, sterile, lyophilized powder that is reconstituted in 0.9% sodium chloride (normal saline). Pixantrone dimaleate, an aza-anthracenedione, is the active ingredient. The structural formula is shown in Figure 13. Its molecular formula is C17 H19 N5 O2 • 2 C4 H4 O4, and the molecular weight is 557.52. The chemical name is 6,9-bis{[(2-amino)ethyl]amino}benzo[g]isoquinoline-5,10-dione dimaleate.

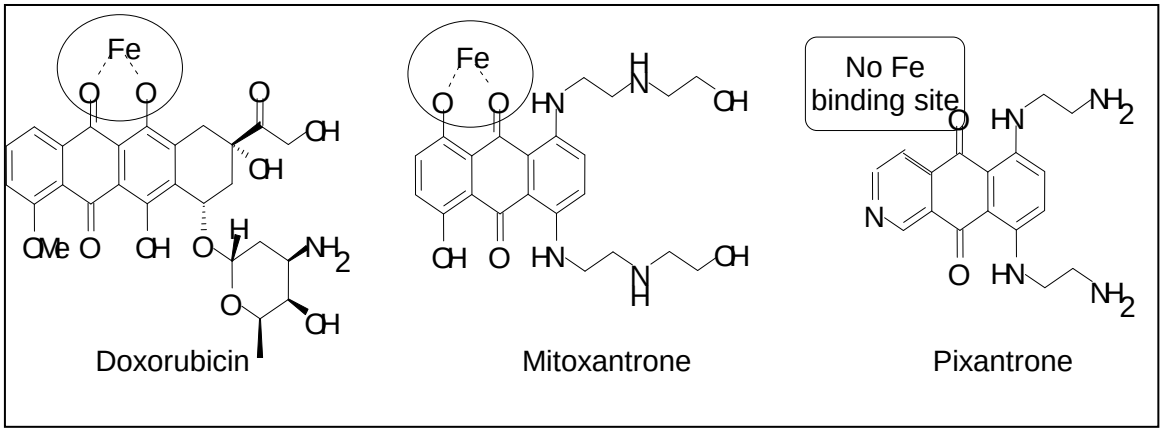
Figure 13 Structural Formula of Pixantrone



2.2 Mechanism of Action

Pixantrone, the first aza-anthracenedione to reach advanced clinical development, was rationally designed to improve the efficacy and reduce the toxicity associated with anthracyclines and anthracenediones by increasing the stability of deoxyribonucleic acid (DNA) adduct formation while reducing the potential to form oxygen free radicals and toxic drug-metal complexes. Unlike mitoxantrone, an anthracenedione, pixantrone lacks the 5,8-dihydroxy-substitution of mitoxantrone and instead contains a nitrogen heteroatom. As shown in Figure 14, the quinine-hydroquinone site responsible for oxygen free radical generation and iron binding in mitoxantrone and doxorubicin is not present in pixantrone.

Figure 14 Comparison of Iron (Fe)-Binding Potential of Doxorubicin, Mitoxantrone, and Pixantrone



These structural changes result in the following significant differences (as reviewed in Borchmann 2005):

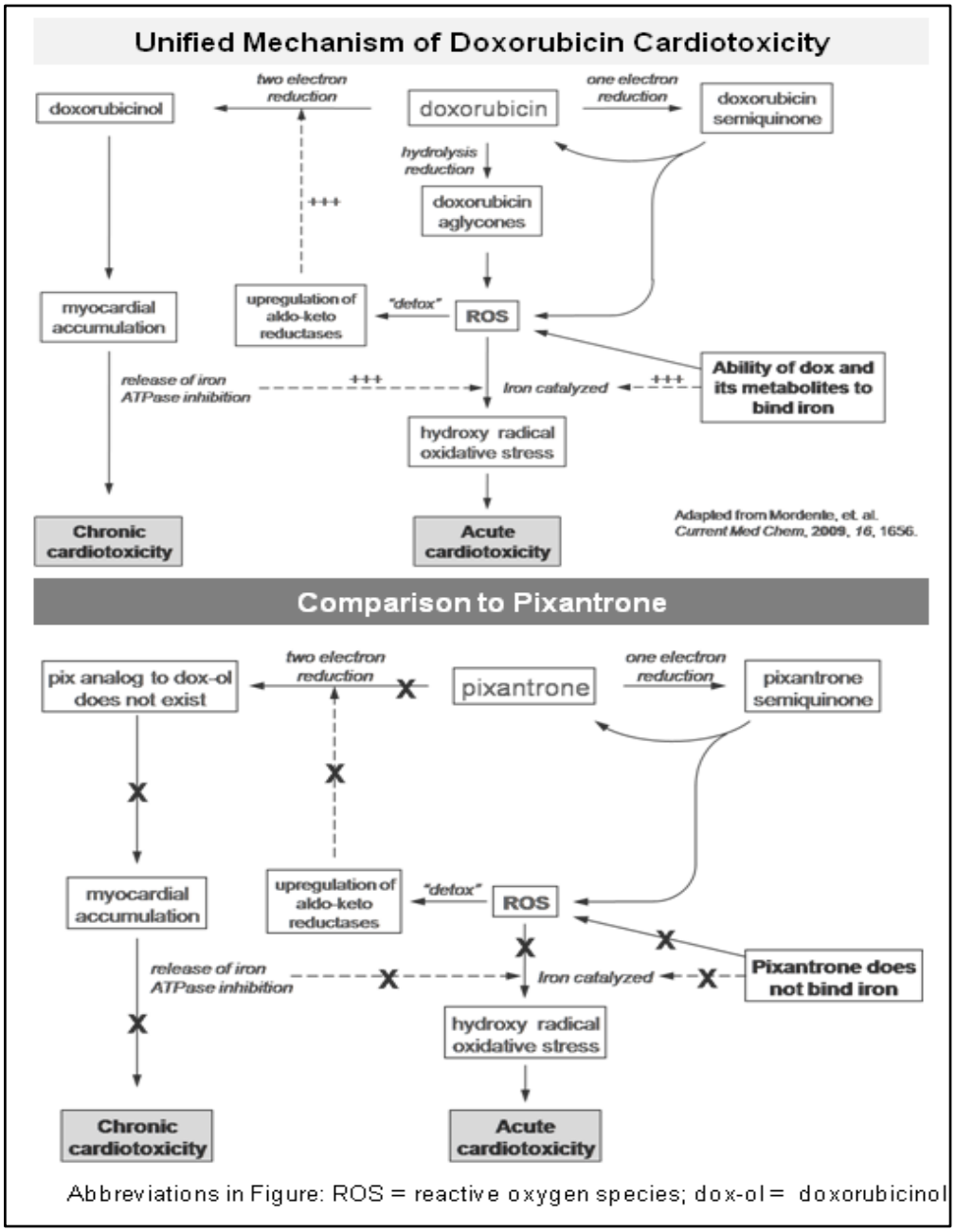
1. Pixantrone is a less avid DNA intercalator than doxorubicin, but becomes a more potent DNA alkylator as a result of the nitrogen substitution in the nucleoside ring; pixantrone chemically bonds to DNA rather than just associating with it. The pixantrone-DNA adducts are formed more rapidly and are more stable than those from mitoxantrone or doxorubicin, theoretically maximizing longer-term DNA damage and antitumor effects.[19]
2. Pixantrone preferentially forms DNA-adducts at methylated CpG sites. This is likely due to an increased affinity on the part of pixantrone for DNA with these sites, which are known to change DNA conformation. Hypermethylation of CpG sites is observed in tumors.[20]

As a direct result of these pharmacological properties, pixantrone is substantially more active and has a broader therapeutic index in leukemia and lymphoma preclinical models than other related drugs.[21]

The cardiotoxicity of first-generation anthracyclines and anthracenediones, such as doxorubicin and mitoxantrone, has been attributed to oxygen free-radical injury mediated by iron-adducts of the anthracycline and its metabolites.[22] The production of these harmful free radicals is enhanced in highly metabolically active organs such as the heart where there is more oxygen and iron and fewer enzymes to destroy these free radicals, making the heart muscle highly susceptible to damage from this class of agents.

The unified mechanism of cardiotoxicity of first generation anthracyclines is shown in Figure 15. First generation anthracyclines can undergo a one electron reduction to produce an anthracycline semi-quinone, or two electron reduction of the carbonyl group to form an alcohol metabolite.

Figure 15 Unified Mechanism of Doxorubicin Cardiotoxicity

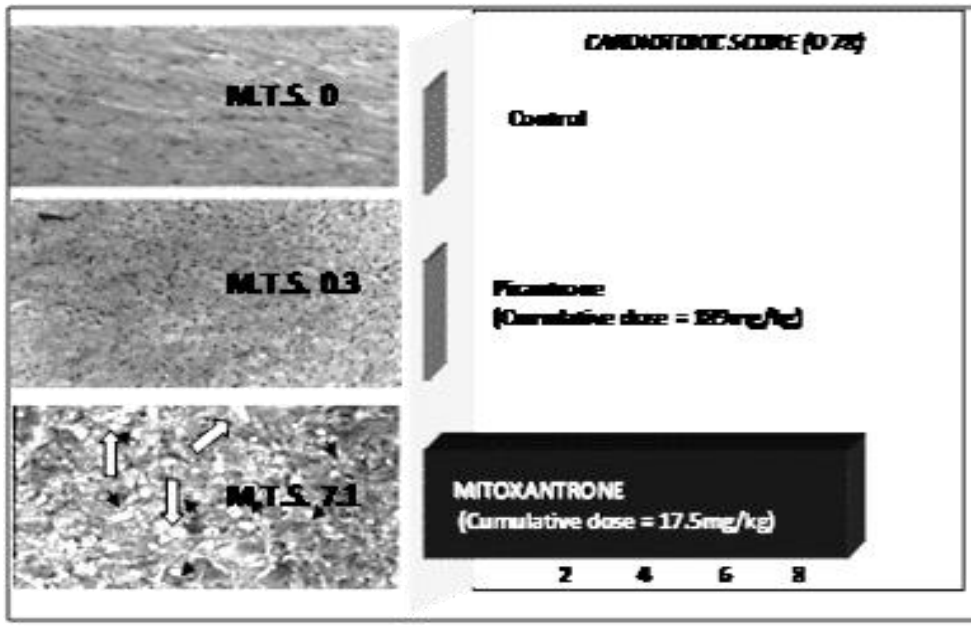


Pixantrone has a different structure and backbone to first generation anthracyclines and anthracenediones. The structural attributes of pixantrone do not allow for several steps associated with the anthracycline cardiotoxicity mechanism since pixantrone cannot undergo a 2 electron reduction, deglycosidation, or form iron adducts. As shown in Figure 15, pixantrone has a lower potential to form and perpetuate the generation of oxygen free radicals than mitoxantrone or doxorubicin. [23]

To explore the cardiotoxic profile of pixantrone, nonclinical studies compared the cumulative effect of pixantrone with that of doxorubicin or mitoxantrone in doxorubicin-pretreated and doxorubicin-naïve animals. Treatment with multiple cycles of pixantrone alone did not cause significant myocardial histologic changes, whereas doxorubicin and mitoxantrone induced the expected myocardial toxicity.[24]

Figure 16 shows the results of one of several studies examining histologic results after repeat doses in anthracycline-naïve mice. Cardiotoxicity was numerically assessed by morphologic evaluation of cardiac lesions for degree of severity (1 or 2) and that number was multiplied by the extension degree (0 to 5, with 0 = no lesions; 5 = most cells damaged) to obtain the total cardiotoxicity score (TCS) for each animal. The mean total score (MTS) was calculated from the mean TCS for each group.[25]

Figure 16 Comparison of Cardiotoxic Score of Pixantrone vs Mitoxantrone



Similar data were obtained when animals were treated with doxorubicin and then retreated with either doxorubicin, mitoxantrone or pixantrone. Pixantrone-treated animals did not worsen their scores whereas mitoxantrone and doxorubicin-pretreated animals developed additional toxicity.

2.3 Pharmacokinetics

The pharmacokinetics (PK) profile of pixantrone (BBR 2778) has been evaluated in 64 patients enrolled in four phase 1 single-agent studies (AZA I-01, AZA I-02, AZA I-03, AZA I-04), and in 72 patients enrolled in three phase 1 studies (AZA I-05, AZA I-06 and AZA I-07) administering pixantrone in combination with other cytotoxic drugs (cytarabine, cisplatin, fludarabine, cyclophosphamide, and vincristine). Pixantrone doses in these studies ranged from 5 to 240 mg/m^2, and the PK of pixantrone did not vary with dose, age or gender. The PK behavior of the drug is highly predictable, based on the linearity with dose and time, together with limited metabolism, weak capability of interaction with the majority of cytochrome P450 (CYP450) substrates, and P-glycoprotein active transporter inhibition. Exposure after repeated doses is not expected to substantially change.

Distribution

Pixantrone is distributed extensively into tissues as indicated by the two volume of distribution terms which are much higher than the total body water (23 L/m^2).[26],[27]. The serum protein binding, determined with [^{14}C]-pixantrone using ultrafiltration technique, was found to be about 57% (Fu=0.43) in humans, a value similar to that measured in animals, and was concentration independent over the tested range of 0.5-30 mg/L.

Elimination

Pixantrone is characterized by a systemic plasma clearance of 20 to 59 L/h/m^2. Renal clearance is a minor elimination route for pixantrone, with urinary excretion accounting for 1.9-9.2% of the administered dose in 0-24 hours. Because of the limited contribution of renal excretion, the compound is assumed in humans, as in animals, to be eliminated by hepatic metabolism and/or excretion in the bile; the clearance, mainly hepatic, approximates the hepatic plasma flow (48 L/h/m^2). [28,29.]

The terminal half-life of pixantrone ranges from 6.2 to 32 hours. These values are rather variable between patients and across studies and are strongly dependent on the time interval

used for estimation. It is reasonable to assume that, for the lowest dosages, the estimated half-life reflects the rapid decline of the first phase.

Metabolism in vitro and in vivo

The qualitative metabolic profile of pixantrone (BBR 2778) was studied in human hepatocytes, liver cytosol and liver microsomes. In human hepatocytes and cytosol, the monoacetylated metabolites BBR 3930 and BBR 3929 were found. These two compounds were also detected in rat hepatocytes and BBR 3929 was the main metabolite found in mouse cytosol. After microsomal incubation, pixantrone underwent an oxidative metabolism, not NADPH/CYP450 mediated, in the side chain resulting in the ring closure to give the compounds BBR 5508 and BBR 5468. The same compounds were also found in dog, rat, and mouse microsomes.

The *in vivo* metabolism of pixantrone was investigated in urine collected up to 24 hours from 5 patients treated at 85 mg/m^2 in the AZA II-01 study.[30] Pixantrone was mainly excreted unchanged and the extent of metabolite excretion was modest in the 0-8 hour collection period. The urinary metabolites were estimated to be less than 5% of the administered dose in a 0-8 hour time interval. Four metabolites were identified in the urine: the monoacetylated compound BBR 3930, the compounds BBR 5508 and BBR 5468 produced by side chain cyclization, and the N-dealkylated derivative NHP 005660. These metabolites were more than 40-fold less potent than the parent drug *in vitro* in human colon cancer cell lines and *in vivo* in disseminated P388 murine leukemia.

In vitro studies found no evidence that pixantrone is a substrate for CYP450 and is only a moderate inhibitor of CYP1A2. Cyclophosphamide and vincristine are substrates of CYP450s, but not of CYP1A2.[31,32] Cisplatin, ARA-C and fludarabine follow different biotransformation routes, not involving CYP450. Therefore, metabolic interactions of such coadministered drugs with pixantrone are considered improbable. Given that pixantrone is weakly bound to plasma proteins, it is unlikely that a displacement phenomenon would occur when administered with highly bound drugs.

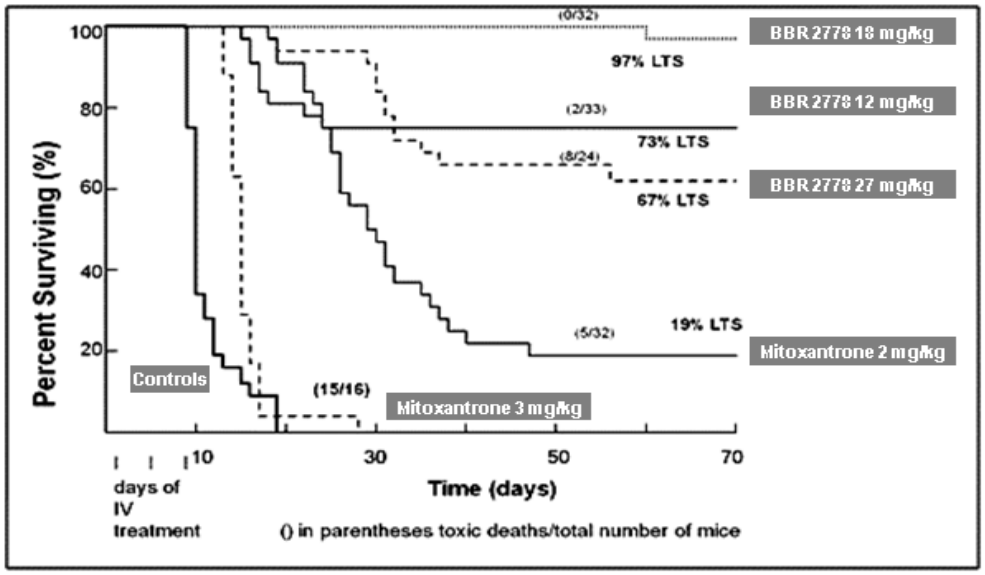
2.4 Nonclinical Overview in Lymphoma

Multiple in vivo hematological tumor models demonstrated the antitumor efficacy of pixantrone. In every animal model, pixantrone was at least equipotent to optimal doses of

mitoxantrone or doxorubicin, and in most models pixantrone had superior efficacy with an attractive therapeutic index (curative at 2/3 its MTD in the YC-8 murine lymphoma model).

In disseminated YC-8 murine lymphoma (Moloney virus induced lymphoma), pixantrone (dosed between 12-27 mg/kg) prolonged survival compared to mitoxantrone (dosed at 2 mg/kg and 3 mg/kg). Pixantrone was consistently more effective than mitoxantrone (Figure 17). The greatest efficacy was observed with pixantrone 18 mg/kg (97% long-term survival), but even with a 33% dose reduction it was more active than mitoxantrone at its most effective dose (2 mg/kg).

Figure 17 Pixantrone (BBR 2778): Increased Survival in YC-8 Murine Lymphoma



3 CLINICAL DEVELOPMENT PROGRAM

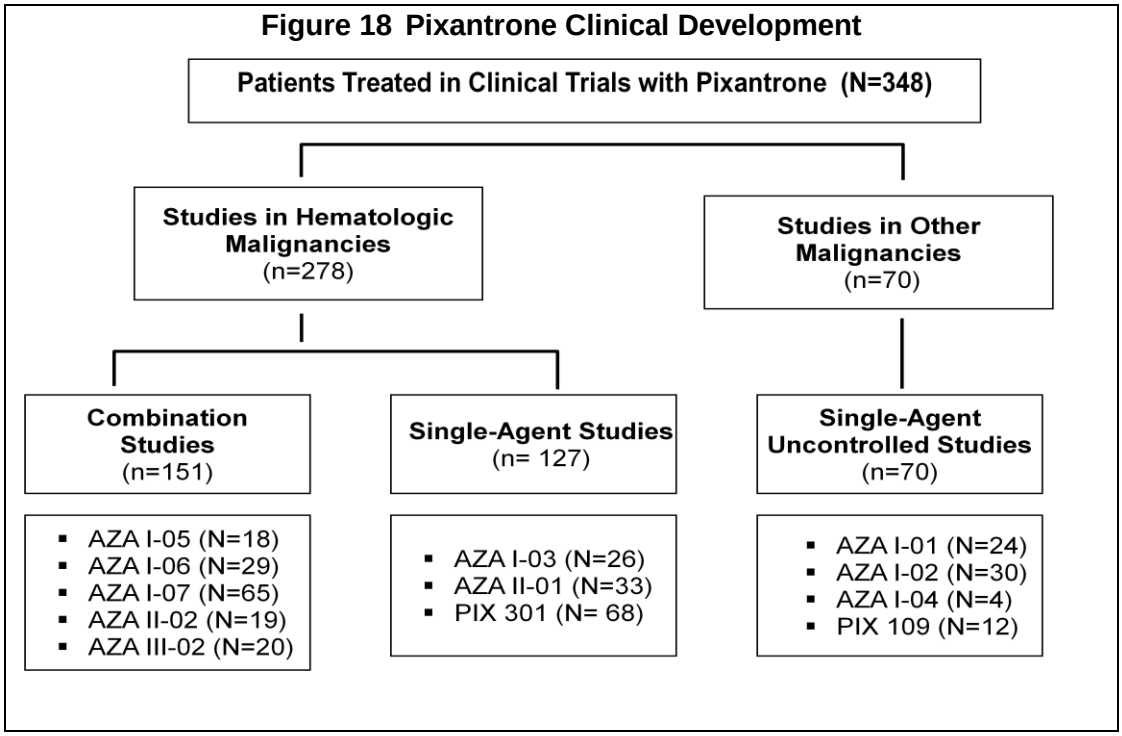
3.1 Clinical Overview of Pixantrone

Pixantrone was synthesized in collaboration with scientists at the University of Vermont and Boerhinger Mannheim Oncology in a programmatic effort to design highly active anthracycline-like molecules with lower potential to form oxygen-free radicals and toxic drug-metal complexes. Following the acquisition of Boerhinger Mannheim by Roche in 1999, the original medicinal chemistry development team (with the rights to pixantrone) formed a new company called Novuspharma Srl. CTI acquired Novuspharma Srl and the rights to

pixantrone (referred to at that time as BBR-2778) and assumed the clinical development of pixantrone in 2004.

The clinical development of pixantrone (Figure 18) includes seven single-agent and five multiagent combination studies which have treated a total of 348 patients with pixantrone; 80% of these patients had NHL and extensive prior anthracycline exposure at the time of study enrollment.

Figure 18 Pixantrone Clinical Development



3.2 Dose Selection and Phase 3 Rationale

Notable antineoplastic activity of pixantrone was observed in phase 1 and 2 studies. Two phase 1 studies, one in patients with relapsed or refractory aggressive NHL (AZA I-03), and one in patients with progressive solid tumors (AZA I-02; [33]) established the maximum tolerated dose (MTD) of single-agent pixantrone using a dose-dense treatment schedule (days 1, 8 and 15 of a 28-day cycle). Both studies identified a MTD based on the incidence of neutropenia, showed a predictable PK, and demonstrated evidence for antitumor activity. In AZA I-03, 23% of 26 aggressive NHL patients achieved an objective response; 4% had a CR; in AZA I-02, 7% of 30 patients with solid tumors achieved an objective response.

The treatment cycle of every 3 weeks in a 4-week cycle as a single-agent was evaluated in Study AZA I-01 in patients with solid tumors; 4% of the 24 patients achieved a response.[34] Additional phase I studies were conducted to define the dose of pixantrone with other commonly used agents in lymphoma, such as with cyclophosphamide, vincristine and prednisone (AZA I-07), with fludarabine, rituximab and dexamethasone (AZA I-06), and with cytarabine, dexamethasone and cisplatin (AZA I-05).

On the basis of safety and activity observed in the single-agent phase I studies in patients with late-stage lymphoma, the dose of 85 mg/m^2 delivered on the dose-dense 3 out of 4 week schedule was further investigated in a phase 2 single-agent study (AZA II-01). Of the 33 patients with relapsed or refractory aggressive NHL enrolled in AZA II-01, 5 (15%) achieved a CR and 4 (12%) achieved a PR for an objective response rate of 27%.[24] Of interest, 5 patients had durable responses with durations of 10.5+, 11+, 15.2+, 17+ and 24+ months.

The rationale for pursuing the phase 3 development of pixantrone as a single agent therapeutic in multiple-relapsed patients with aggressive NHL included:

- The high rate and durability of complete response in heavily pretreated patients with relapsed and refractory aggressive NHL
- The lack of consensus regarding treatment standards for patients with refractory or multiply relapsed aggressive NHL and the need for a therapeutic option with rigorously defined efficacy
- The demonstrated efficacy (ORR 27%; CR rate 15%) and tolerability of pixantrone in the single-arm phase 2 study AZA II-01, with the 5 CRs achieved in this trial demonstrating response durations greater than 10 months.
- The assessment that a controlled trial comparing pixantrone to other potentially effective single agents would better define safety and efficacy than a comparative combination study or a single-agent trial without a comparator group

3.3 Phase 3 Study – PIX301

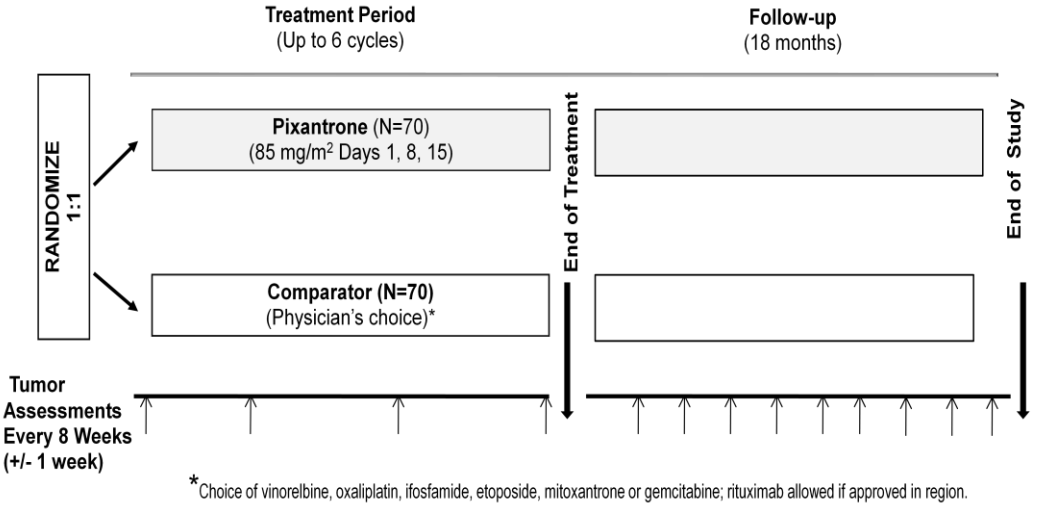
A randomized phase 3 trial (PIX301) was designed to evaluate the activity of pixantrone as single-agent therapy in patients with aggressive relapsed or refractory NHL who had received two or more prior lines of therapy. Pixantrone was granted fast track designation for

this patient population by the FDA, acknowledging an unmet medical need.

3.3.1 Overall Study Design

PIX301 was a randomized, active-control, multicenter, open-label study comparing single-agent treatment with pixantrone to other prespecified single-agents (based on the physician's choice) in patients with relapsed or refractory aggressive NHL who had received two or more lines of therapy (Figure 19).

Figure 19 PIX301 Study Design



As no therapy has been approved or is considered standard in the third-line setting, patients who had received at least two lines of multiagent regimens were, as such, exposed to a broad variety of active agents. Providing a selection of comparator agents allowed physicians to choose an agent most likely to benefit patients randomized to the comparator arm.

Comparator Agents

- oxaliplatin 100 mg/m^2 IV day 1 of each 21-day cycle for up to 6 cycles
- ifosfamide 3 g/m^2 IV days 1 and 2 of 28-day cycles for up to 6 cycles
- vinorelbine 30 mg/m^2 IV days 1, 8, 15, and 22 of 28-day cycles for up to 6 cycles
- etoposide either 100 mg/m^2 IV days 1-5 of 28-day cycles, OR 50 mg/m^2 orally days 1-21 of 28-day cycles, for up to 6 cycles
- mitoxantrone 14 mg/m^2 IV day 1 of 21-day cycles for up to 6 cycles

- gemcitabine 1250 mg/m^2 IV days 1, 8 and 15 of 28-day cycles for up to 6 cycles
- rituximab 375 mg/m^2 IV at increasing rates days 1, 8 and 15 of cycle 1 and day 1 of cycle 2 in CD20+ patients only

A total of 140 eligible patients were randomized in a 1:1 ratio to receive either pixantrone 85 mg/m^2 by intravenous infusion on days 1, 8 and 15 of 28-day cycles for up to 6 cycles or a comparator at the dose and schedule as described above. Stratification randomization with dynamic block was used. There were three stratification factors: region (North American vs. Western Europe vs. Rest of World), International Prognosis Index (IPI) Score (0, 1 vs ≥ 2), and prior stem cell transplant (yes vs no).

After receiving up to 6 cycles of treatment, all patients were asked to enter into an 18-month follow-up period. The detailed study schedule and evaluation can be found in Appendix 1.

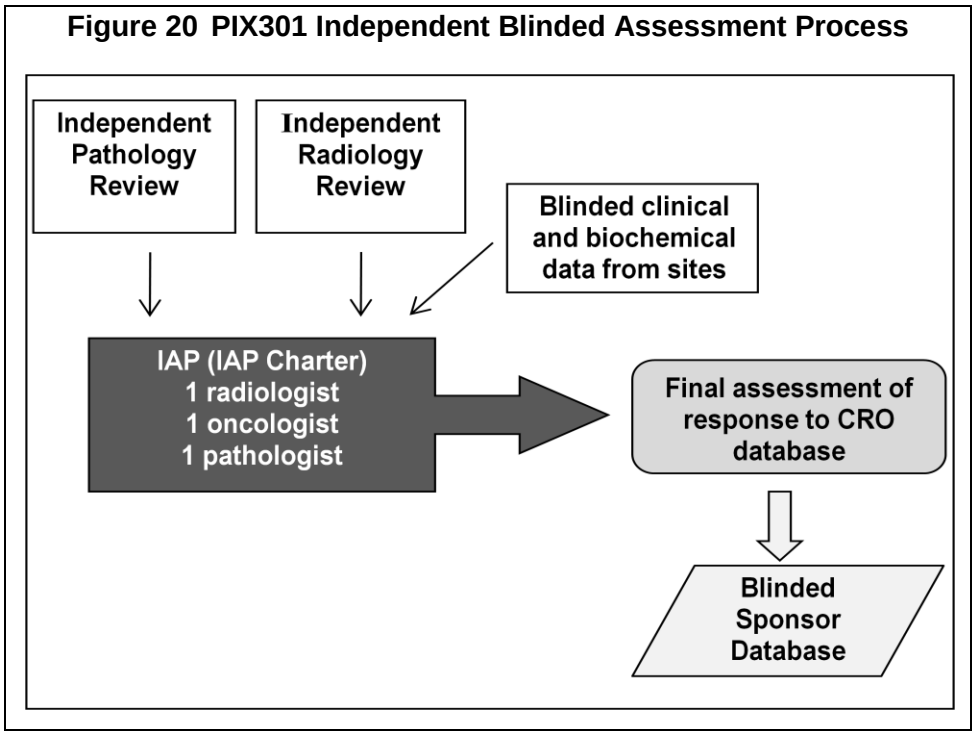
3.3.2 Independent Assessment of Tumor Response and Disease Progression

The PIX301 study incorporated independent radiology review, guided by a charter, to assure an objective, blinded, unbiased, and scientifically rigorous evaluation of images used to assess responses. Expert board-certified radiologists, who were blinded to subject confidential identifiers, investigator site identifiers, site lesion selection for tumor assessments, site determination of tumor response, clinical outcome and study treatment assignment, assessed study CT (or MRI) examinations and determined tumor response at protocol-specified time-points.

Independent pathology review was similarly performed under a charter. Two independent pathologists reviewed each baseline lymph node biopsy or tissue to confirm the diagnosis of aggressive NHL; if there was a disagreement, the specimen was assessed by a third pathologist and the majority assessment prevailed. An independent pathologist also reviewed the bone marrow biopsy and/or aspirate to determine bone marrow involvement at baseline.

As shown in Figure 20, the final assessment of response (primary endpoint) was determined by a separate independent assessment panel (IAP) consisting of one radiologist, one oncologist and one pathologist.

Figure 20 PIX301 Independent Blinded Assessment Process



The members of the IAP were guided by a charter and operated independently from CTI as well as from the investigators. The IAP was blinded to patient treatment assignment and investigator's assessment of response. The IAP based their assessment on:

- Review of imaging and qualitative evaluation of the independent radiology assessment. If the IAP radiologist did not agree with the original independent radiologist's assessment of response, the IAP assessment was used.
- The independent pathologist's assessment of bone marrow involvement
- Clinical and biochemical data

At each IAP meeting, the oncologist and radiologist first evaluated the data specified above to determine the subject's response at each protocol-specified timepoint. Following this, the pathologist reviewed the assessments made by the radiologist and oncologist. In the event that the IAP members were not in agreement on a subject's response, the majority opinion prevailed. If a majority was not reached, the lowest level of response was assigned. If data existed for timepoints subsequent to an IAP assessment of response of progressive disease

(PD), the IAP continued to assess response for these later timepoints.

3.3.3 **PIX301 Study Population**

Major Inclusion criteria

1. Histologically-confirmed aggressive (de novo or transformed) NHL according to REAL/WHO classification using investigator's institutional pathologic assessment to determine eligibility. Lymph node biopsy slides or tissue blocks suitable for review were to be available and sent for central retrospective review after randomization.
2. Types of NHL permitted were:
   - diffuse large B-cell lymphoma (DLBCL, included mediastinal large B-cell lymphoma and primary effusion lymphoma/immunoblastic lymphoma)
   - transformed indolent lymphoma (areas of follicularity allowed)
   - peripheral T-cell lymphoma (not otherwise specified; included diffuse mixed cell lymphoma)
   - follicular lymphoma – grade III
   - anaplastic large cell lymphoma (T/null cell or primary systemic type)
3. Patients with any Ann Arbor stage, IPI score, or bone marrow status were eligible.
4. At least one objectively measurable lesion as demonstrated by CT, spiral CT, or MRI that could be followed for response as a target lesion.
5. Relapse (with evidence of disease progression) after 2 or more prior chemotherapeutic or chemotherapeutic + immunotherapeutic regimens, which included first-line treatment with an anthracycline-containing regimen such as CHOP or a CHOP-equivalent. In countries where rituximab was the standard of care and available at the patient's institution, patients who were CD20+ at the time of initial diagnosis were required to have previously received that agent.
6. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
7. Left ventricular ejection fraction ≥ 50% as determined by MUGA scan

Major Exclusion Criteria

1. Prior treatment with a cumulative dose of doxorubicin or equivalent exceeding 450 mg/m² according to the calculation index: X/450 + Y/160 > 1, where X was the doxorubicin dose in mg/m^2 and Y the mitoxantrone dose in mg/m^2
2. Active CNS lymphoma involvement based on clinical evaluation
3. Histological diagnosis of Burkitt lymphoma, lymphoblastic lymphoma, or mantle cell lymphoma.
4. Clinically significant cardiovascular abnormalities (equal to NYHA grade III- IV), myocardial infarction within the prior 6 months, severe arrhythmia, uncontrolled hypertension, or uncontrolled angina

3.3.4 Study Enrollment Challenges

A total enrollment of 320 patients was originally planned. There were 189 sites activated worldwide, of which only 66 sites enrolled patients.

The study was opened in June 2004, with initially a planned enrollment period of 18 to 24 months. Efforts to increase enrollment included expanding the eligible patient population by implementing several protocol amendments including permitting enrollment of patients with NYHA functional Class II impairment, decreasing the washout period before enrollment from 4 to 2 weeks, allowing enrollment of patients with a history of certain cancers provided the disease-free interval was at least 5 years, permitting the use of intrathecal chemotherapy in high-risk patients, and adding follicular lymphoma grade III to the inclusion criteria.

Despite these protocol amendments to increase the eligible patient population, as well as aggressive attempts to enhance enrollment by expanding the number of countries from 11 to 24, increasing site activation from 90 to 189 sites, and hiring additional regional CROs, enrollment remained slow and challenging. Study enrollment was ultimately stopped in March 2008 after the enrollment of 140 patients in the intent-to-treat population. The sponsor remained blinded to study results until database lock in February of 2009.

3.4 Statistical Methods

Statistical analysis methodology remained unchanged from the statistical analysis plan submitted and reviewed by the FDA in the SPA review process.

Two databases were submitted to the FDA from the PIX301 study.

- The first database used to support the NDA filing included all data up to the data cutoff of 30 September 2008, which occurred after the last patient completed the end-of-treatment visit.
- At the time of the 120-Day safety update, a second database was submitted encompassing all safety and efficacy data with a cutoff date of 25 June 2009. This database included data from all treatment periods and a minimum of 9 months of follow-up data. The 18-month follow-up period of the study is still ongoing.

Per the statistical analysis plan, the ITT population, which included all randomized patients, was the primary population for all efficacy evaluations. Secondary efficacy analyses utilizing the retrospective independent histologic assessments (HITT population), as well as response by investigator assessment, were also conducted as supportive analyses. Safety analyses were based on the safety population, defined as all randomized patients who received at least one dose of study medication.

3.4.1 Hypothesis

The study was designed to test the hypothesis that single-agent pixantrone would achieve a superior CR/CRu rate versus comparator agents in patients with relapsed or refractory aggressive NHL who had received two or more lines of prior therapy.

3.4.2 Power and Sample Size Determination

Initial power and sample size assumptions were based on study AZA II-01, a single-arm study of single-agent pixantrone, in which the CR rate was 15%. There were limited data available in the literature on the third-line setting. It was believed that the CR/CRu rate with comparators was ≤ 5%. Assuming a CR/CRu rate of 15%, the study was designed to detect a 10% difference on CR/CRu rate between the two treatments and required a total of 320 patients (160 per arm) to achieve 80% power.

With the enrollment of 140 patients, the study was sufficiently powered (approximately 80%) to detect a 15% difference in the CR/CRu rate, assuming an 18% CR/CRu rate in the pixantrone arm.

3.5 Efficacy Evaluations

3.5.1 Primary Endpoint: CR/CRu Rate

The primary endpoint, CR/CRu (complete response and unconfirmed complete response) rate, was defined as the proportion of all randomized patients (ITT population) with CR or CRu as assessed by the IAP according to the International Workshop to Standardize Response Criteria for NHL (Appendix 2). The primary analysis was based on the ITT population by IAP assessment through EOT. Fisher exact test was used to compare the difference of the response rates between the pixantrone and comparator groups.

3.5.2 Secondary Endpoints

3.5.2.1 *Overall Response Rate (ORR)*

The overall response rate (ORR) was defined as the total proportion of patients with CR, CRu or PR. It was analyzed in the same manner as the CR/CRu rate.

3.5.2.2 *Responses Lasting at Least 4 Months*

This secondary endpoint was defined as the percentage of patients who achieved a response (CR, CRu, or PR) with a duration of response at least 4 months. The duration of response was calculated from the first documented response to disease progression or death. If a patient achieved response but did not reach progression or death by the time of database cutoff, this patient was counted in this endpoint.

3.5.2.3 *Duration of Response*

Duration of response (CR, CRu, PR) was defined as the time from the first documented response to disease progression/relapse or death. Patients who had neither progressed nor died had their duration censored at the date of their last disease assessment. A patient receiving a new treatment for aggressive NHL (including induction treatment for transplant), in the absence of a documented progression, was considered as progressing at the time of the new treatment. Patients who were still responding at the date of their last tumor assessment were censored at the date of last tumor assessment. Patients who were not assessed for efficacy or did not achieve a documented response were censored at the date of randomization.

In addition, duration of CR/CRu was analyzed in a similar manner.

3.5.2.4 *Progression-Free-Survival (PFS)*

Progression-free survival, a secondary endpoint, was defined as the time from randomization to the initial documentation of progressive/relapsed disease or death due to any cause. In the PFS analysis, patients who received additional lymphoma-directed therapy without documented progression were considered as having an event.

Patients who were alive and without disease progression at their date of last tumor assessment were censored at the date of last tumor assessment. Patients who did not progress prior to the end of the study or discontinue for other reasons were censored at that time. Patients who were not assessed for efficacy were censored at the date of randomization. Kaplan-Meier estimation was used to evaluate PFS. Unstratified log-rank test was used to compare the difference on PFS between the two treatment groups.

In addition, subgroup analyses were performed based on baseline prognostic factors (age group, IPI score, prior anthracycline exposure, prior rituximab exposure, etc). Sensitivity analyses were performed to evaluate different censoring strategies.

3.5.2.5 *Overall Survival (OS)*

Overall Survival was defined as time from randomization to death due to any cause. The statistical method used for OS was similar to that used for PFS. OS was analyzed at the two database cutoff points described above. The final OS analysis will be conducted after the last patient completes follow-up.

3.5.2.6 *Prespecified Supportive Analyses*

Secondary analyses included investigator assessments of response as well as applying the IAP response assessments to a retrospective independent central review of histology, referred to as the HITT population. Additional CR/CRu responses occurring during the follow-up period without additional therapy were also evaluated as supportive analyses.

3.5.3 **Single-Blind**

Although this study was designed as an open-label study, it was open-label only to the investigator and patients enrolled in the study. The sponsor followed procedures similar to

those used in a double-blind study and remained blinded during the entire treatment period. The randomization schedule was housed at, and implemented by, an independent CRO. Data management and analyses were performed by an independent CRO. All assessments of histology and response by both the IRC and IAP were also blinded to treatment assignment.

3.5.4 Interim Analysis

Two interim analyses were originally planned and outlined in the SAP and DMC charter. A futility analysis was scheduled when 40 patients had completed two cycles of therapy. The DMC deliberated in closed sessions (excluding CTI and the CRO) on whether the study should close for futility or continue. The DMC informed the Sponsor of its decision to continue the study as planned.

An interim efficacy analysis when the study had enrolled 160 patients was originally planned and outlined in the SAP and DMC charter. Due to the decision to halt enrollment to the study, the planned interim analysis at the study midpoint was no longer applicable and was not conducted. Therefore, no type I error adjustment was required.

3.6 Regulatory History

Since assuming pixantrone clinical development responsibility in 2004, CTI has interacted with FDA for the later phase of its clinical development program. Table 4 summarizes the major regulatory interactions between CTI and the FDA regarding the clinical development of pixantrone.

Table 4 Major Regulatory Interactions in the Development of Pixantrone

Interactions and Activities	Date
Investigational New Drug (IND) 62,678 submitted by Novuspharma	May 2001
End-of-Phase II meeting with FDA	October 2003
Special Protocol Assessment (SPA) application submitted for Study PIX301	January 2004
CTI-FDA interactions on SPA	February 2004 & March 2004
PIX301 Statistical Analysis Plan (SAP) and Case Report Forms (CRFs) submitted to FDA	June 2004
Fast-Track designation for 3rd-line treatment of relapsed, aggressive NHL approved by FDA	July 2004
CTI discussed the possibility of stopping study with FDA	July 2007
CTI notified FDA of decision to halt enrollment in Study PIX301 due to very slow enrollment rate	March 2008
SAP revised to reflect early halt of enrollment and cancellation of planned interim analysis submitted to FDA (although sample size reduced, the statistical methods for data analyses remained the same)	May 2008
CTI submitted preliminary efficacy data to FDA in request for a pre-NDA meeting	December 2008
FDA sent written response that adequate efficacy data exists to support NDA filing	January 2009
CTI began and completed rolling NDA 22-481	April - June 2009
FDA accepted the NDA for filing	August 2009
CTI requests accelerated approval	November 2009

During the development of pixantrone, CTI sought the advice of the FDA's Division of Oncology Drug Products (DODP) in a series of meetings and other interactions related to the phase 3 program in aggressive NHL. Requirements for registration in relapsed, refractory aggressive NHL were initially addressed in an end-of-phase 2 meeting, and during the Special Protocol Assessment (SPA) interactions, agreements were reached on the following:

- Patient population suitable for a randomized trial design
- Selection of CR/CRu as the primary endpoint and selection of secondary endpoints (duration of response, overall response, PFS and OS)

- Choice of comparator agents
- Statistical analysis plan

In July 2007, CTI discussed with FDA the possibility of halting the phase 3 study, PIX301, because of slow enrollment. (See a discussion of enrollment efforts in section 3.3.4). In March 2008, after enrolling 140 patients between June 2004 and March 2008 for an enrollment rate of 3.1 patients per month, CTI notified FDA of their decision to halt enrollment in PIX301 due to the inability to alter enrollment rates adequately to achieve the planned target of 320 patients within a reasonable timeframe. In May 2008, CTI submitted to the FDA a revised PIX301 statistical analysis plan to reflect the early halt of enrollment and cancellation of the planned interim analysis. Although the sample size was reduced, the original statistical analysis plan and statistical methods for data analyses, previously agreed upon with the FDA, remained the same.

Additional discussions concerning the registration trial occurred between CTI and DODP during the conduct of PIX301. In January 2009, CTI received preliminary responses from FDA to questions posed for a scheduled pre-NDA meeting. FDA agreed that the efficacy data presented appeared to support an NDA filing and concurred that the number of subject exposures at the proposed dose and schedule within the intended patient population appeared adequate to support an NDA filing.

The NDA was submitted to FDA for review on a rolling basis between April and June 2009 for pixantrone as single-agent treatment for patients with relapsed or refractory aggressive NHL who had received two or more prior lines of therapy. The NDA was accepted for filing in August 2009. In November 2009, following a post-submission meeting with the FDA on October 23 2009, a request was submitted for consideration for accelerated approval.

3.7 Summary of Efficacy of Pixantrone

The pivotal study PIX301 successfully met its primary efficacy endpoint, with 20% of pixantrone recipients achieving a CR/CRu compared to only 5.7% of patients who were treated with comparator agents (p=0.021). No patients (0%) in the comparator arm achieved a confirmed complete response compared to 8 patients (12%) of pixantrone recipients. This section summarizes the efficacy results of this study.

3.8 Patient Characteristics

3.8.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics of patients enrolled in PIX301 were well-balanced between the two treatment arms, as shown in Table 5.

Table 5 Demographic and Baseline Characteristics (ITT Population)

	Pixantrone (N=70)	Comparator (N=70)
Age (years)		
Mean (SD)	58.2 (13.5)	56.2 (12.9)
Median (range)	60.0 (18-80)	58.0 (26-82)
Age category, n (%)		
≤60 years	38 (54.3%)	41 (58.6%)
>60 years	32 (45.7%)	29 (41.4%)
Sex, n (%)		
Male	46 (65.7%)	40 (57.1%)
Female	24 (34.3%)	30 (42.9%)
Race, n (%)		
Caucasian	46 (65.7%)	44 (62.9%)
Non-Caucasian	24 (34.3%)	26 (37.1%)
Baseline ECOG Performance Status, n (%)		
0	26 (37.1%)	23 (32.9%)
1	30 (42.9%)	32 (45.7%)
≥ 2	14 (20.0%)	15 (21.4%)
Geographic Region, n (%)		
North America	4 (5.7%)	4 (5.7%)
Western Europe	19 (27.1%)	19 (27.1%)
Rest of World	47 (67.1%)	47 (67.1%)
Weight (kg)		
Mean (SD)	70.8 (15.75)	68.7 (15.34)
Median (range)	70.0 (45-117)	69.0 (37-115)

Source: PIX301 CSR Table 14.1.6
Fisher exact test was used to compare proportions between groups, and a two-sided student's t-test was used in the comparison of means between treatment groups. No differences were statistically significant.

3.8.2 Baseline Disease Characteristics

Initial diagnosis and baseline NHL disease characteristics were well balanced between the two treatment groups (Table 6). A majority of the patients (75%) had DLBCL, 14% had transformed indolent lymphoma, 7% had T-cell NHL, 2% had anaplastic large cell lymphoma, and 2% had follicular grade III lymphoma as determined by local institutional pathologists. Most patients (76%) had Ann Arbor stage III or IV disease, and 74% of the patients had IPI scores ≥ 2. The median duration of NHL was about 32 months, ranging from 7 to 160 months among pixantrone recipients and from 0 to 333 months for patients randomized to the comparator arm. A higher percentage of patients in the comparator group (63%) had a response to their last therapy prior to randomization versus those randomized to pixantrone (51%).

Table 6 Baseline NHL Disease Characteristics (ITT Population)

	Pixantrone (N=70)	**Comparator (N=70)**	**P-value[1]**
Duration of NHL (months)			
Mean (sd)	43.6 (35.6)	46.6 (51.7)	*0.693*
Median (range)	32.0 (7-160)	31.6 (0-333)	
Histology, n (%)			
Transformed indolent lymphoma	10 (14.3%)	9 (12.9%)	*0.711*
Diffuse large B-cell lymphoma	54 (77.1%)	51 (72.9%)	
Peripheral T-cell lymphoma	3 (4.3%)	7 (10.0%)	
Anaplastic large cell lymphoma, null cell, primary systemic type	2 (2.9%)	1 (1.4%)	
Follicular lymphoma grade III	1 (1.4%)	2 (2.9%)	
Ann Arbor Stage of NHL, n (%)			
I/II	19 (27.1%)	14 (20.0%)	*0.426*
III/IV	51 (72.9%)	56 (80%)	
International Prognostic Index, n (%)			
0 -1	20 (28.6%)	17 (24.3%)	*0.949*
2	25 (35.7%)	27 (38.6%)	
≥ 3	25 (35.7%)	25 (35.7%)	
Missing	0	1 (1.4%)	

Table 6 Baseline NHL Disease Characteristics (ITT Population)

	Pixantrone (N=70)	Comparator (N=70)	P-value[1]
Number of Extranodal Sites, n (%)			
0	35 (50.0%)	35 (50.0%)	*1.00*
≥1	34 (48.6%)	33 (47.1%)	
Missing	1 (1.4%)	2 (2.9%)	
Time from Start of Most Recent Chemotherapy to Randomization (months)			
Mean (SD)	13.6 (15.7)	13.4 (23.5)	*0.941*
Median (range)	8.8 (1-86)	8.5 (1-190)	
Response to Most Recent Chemotherapy, n (%)			
CR/CRu/PR	36 (51.4%)	44 (62.8%)	*0.356*
SD/PD	31 (44.3%)	26 (37.1%)	
Missing	3 (4.3%)	0	

Source: PIX301 CSR Table 14.1.7
[1] Fisher exact test was used to compare proportions between the groups, and a two-sided student's t test was used to compare means between treatment groups. P-values are for reference purposes only.

Study inclusion criteria required that patients had received at least two prior lines of therapy, with the majority of patients in both treatment groups having received three or more prior lines of therapy (Table 7). All patients received prior anthracycline-like agents (doxorubicin, mitoxantrone). The median lifetime exposure to anthracyclines and related compounds prior to beginning the study was similar between the pixantrone and comparator groups (292.9 and 315.5 mg/m^2).

About 55% of patients (54.3% and 55.7% in the pixantrone and comparator arms, respectively) had received prior anti-CD20 treatment as rituximab alone, as part of a chemotherapy regimen, or as a component of a radioimmunotherapeutic regimen, including 64 of 105 DLBCL patients who received 1 or more anti-CD20 based regimens. Fifty-seven percent of patients in each arm were refractory to their last treatment regimen (relapse within 8 months of initiation of therapy).

Table 7 Prior NHL Treatment (ITT Population)

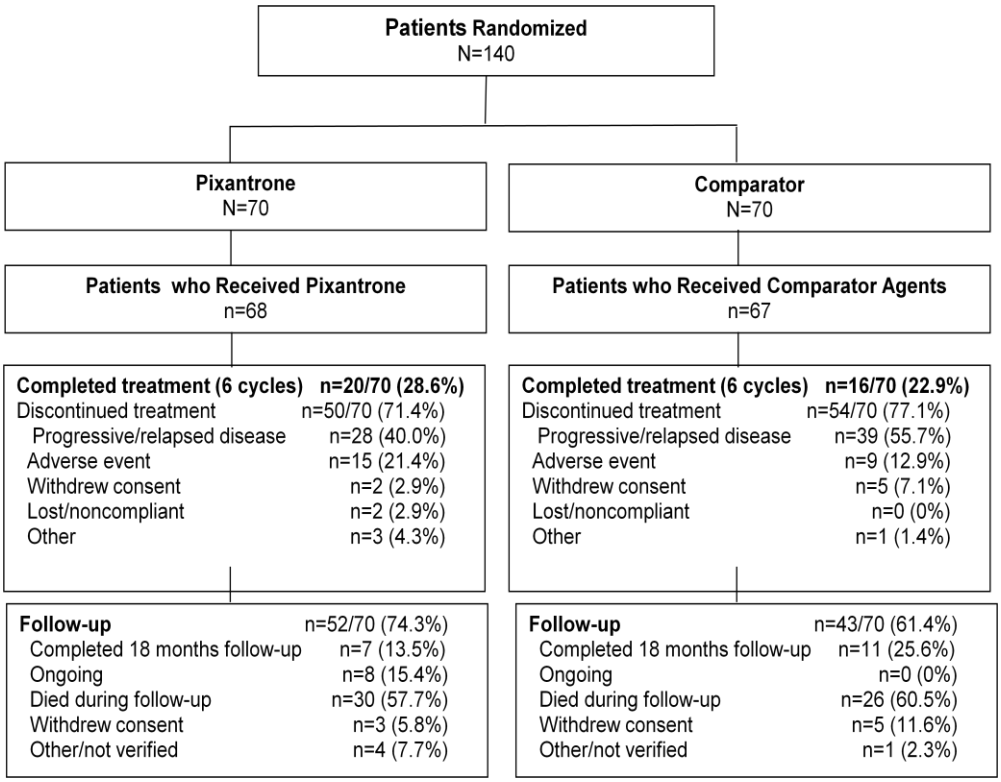
	Pixantrone (N=70)	Comparator (N=70)	P-value
Prior Chemotherapy Regimens, n (%)			
2	32 (45.7%)	24 (34.3%)	*0.559*
3	24 (34.3%)	33 (47.1%)	
≥ 4	14 (20.0%)	13 (18.6%)	
Patients Who Received Prior SCT, n (%)			
Yes	11 (15.7%)	10 (14.3%)	*1.00*
No	59 (84.3%)	60 (85.7%)	
Number of Prior Chemotherapy Regimens			
Mean (SD)	2.9 (1.25)	3.0 (1.2)	*0.626*
Median (range)	3.0 (2-9)	3.0 (2-8)	
Patients who Received Prior Biologic Therapy (anti-CD20), n (%)			
Yes	38 (54.3%)	39 (55.7%)	*1.00*
Prior Anthracycline Dose Equivalent (mg/m2)[1]			
Mean (SD)	292.6 (118)	326.6 (135)	*0.116*
Median (range)	292.9 (51-472)	315.5 (15-681)	
Refractory/Relapsed Category, n (%)			
Refractory	40 (57.1%)	40 (57.1%)	*0.544*
Relapsed	28 (40.0%)	30 (42.9%)	
Response to Most Recent Therapy, n (%)			
CR/CRu	17 (24.3%)	18 (25.7%)	*0.356*
PR	19 (27.1%)	26 (37.1%)	
SD	9 (12.9%)	6 (8.6%)	
PD	22 (31.4%)	20 (28.6%)	
Missing	3 (4.3%)	0 (0%)	

Source: PIX301 CSR Table 14.1.7 and 14.1.8
Fisher exact test was used to compare proportions between the groups, and a two-sided student's t test was used to compare means between treatment groups. P-values are for reference purposes only.

3.8.3 Patient Disposition

Of the 140 patients enrolled, 36 patients completed protocol-defined 6-cycles of treatment (20 in the pixantrone group and 16 in the comparator group).

Figure 21 PIX301 Patient Disposition



The reasons patients discontinued study treatment are summarized in Figure 21. The most common reason for discontinuing study treatment was progressive or relapsed disease (40% in pixantrone group vs 56% in comparator group). Fifteen (21%) pixantrone patients compared with 9 (13%) comparator patients discontinued due to adverse events. Treatment was to be discontinued for patients on either arm with LVEF decreases ≥ 20 percentage points from baseline values, a decline in LVEF to ≤ 40%, or clinical signs or symptoms of congestive heart failure.

3.9 Efficacy Results

3.9.1 Primary Endpoint: CR/CRu Rate

PIX301 met its protocol defined primary efficacy endpoint. The primary analysis, as prospectively defined, was based on the IAP assessment of response in the ITT population. By the end of treatment period, 20% (14/70) of patients in the pixantrone group achieved a CR/CRu, compared with 6% (4/70) of patients in the comparator group (Table 8). This finding was statistically significant (p= 0.021). Eight patients in the pixantrone group achieved a confirmed CR, compared with no patients in the comparator group.

Table 8 Summary of CR/CRu per IAP Assessment (ITT Population) – Primary Efficacy Endpoint

Data Cutoff 30 Sep 2008

	Pixantrone (N=70)	**Comparator (N=70)**	***P*-value**
CR/CRu, n (%) (95% CI)	14 (20.0%) (11.4%, 31.3%)	4 (5.7%) (1.6%, 14.0%)	*0.021*
CR, n (%)	8 (11.4%)	0 (0%)	
CRu, n (%)	6 (8.6%)	4 (5. 7%)	

Source: PIX301 CSR Table 14.2.1 and 14.2.7
Fisher exact test was used to compare proportions in the pixantrone and comparator groups.

3.9.2 Overall Response Rate (ORR)

The overall response rate, defined as the total proportion of patients with a CR, CRu or PR, was significantly higher in the pixantrone group than in the comparator group (37% vs 14%; *P* = 0.003) based on ITT population (Table 9).

Table 9 Overall Response Rate (CR, CRu, PR) per IAP Assessment (ITT Population)
Data Cutoff 30 Sep 2008

	Pixantrone (N=70)	**Comparator (N=70)**	***P*-value**
ORR	26 (37.1%)	10 (14.3%)	*0.003*
Source: PIX301 CSR Table 14.2.27 Fisher exact test was used to compare proportions in the pixantrone and comparator groups.			

3.9.3 Responses Lasting ≥ 4 Months

The percentage of patients with a response (CR, CRu, PR) lasting at least 4 months was a measurement of both frequency and durability of responses. Patients were counted if they had a CR, CRu, or PR with a duration of at least 4 months from the first documented objective response to disease progression or death. A higher percentage of patients who were in the pixantrone group had objective responses lasting at least 4 months compared to patients in the comparator group (26% vs 9%, p=0.012).

3.9.4 Duration of Response

3.9.4.1 *Duration of ORR*

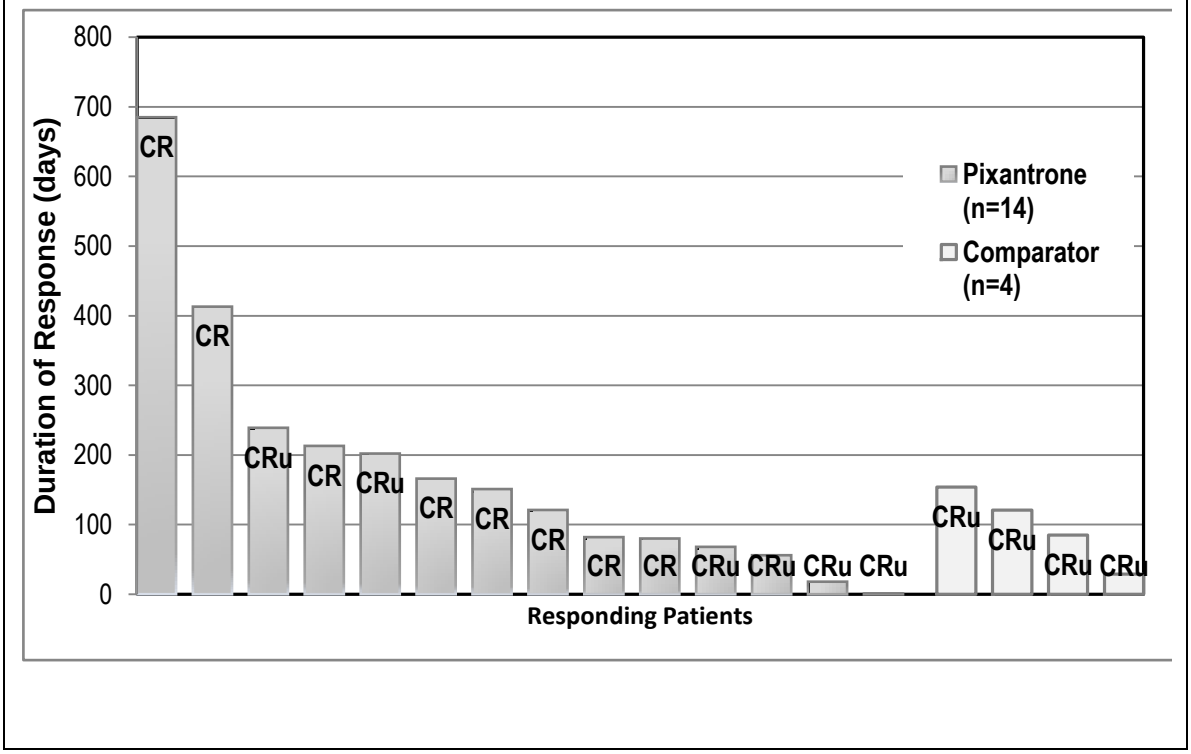
The median duration of overall response (CR, CRu, PR) was 5.0 months for the pixantrone group and 4.5 months in the comparator group (HR=0.595, p=0.22, 95% CI 0.026, 1.37).

3.9.4.2 Duration of CR/CRu

Median duration of CR/CRu was 7 months for the pixantrone group and 3.4.months in the comparator group (HR 0.25, p=0.033,95% CI 0.06, 1.01). Duration of CR/CRu by patient is shown in Figure 22.

Figure 22 Duration of CR/CRu by Patient IAP Assessment (ITT Population)

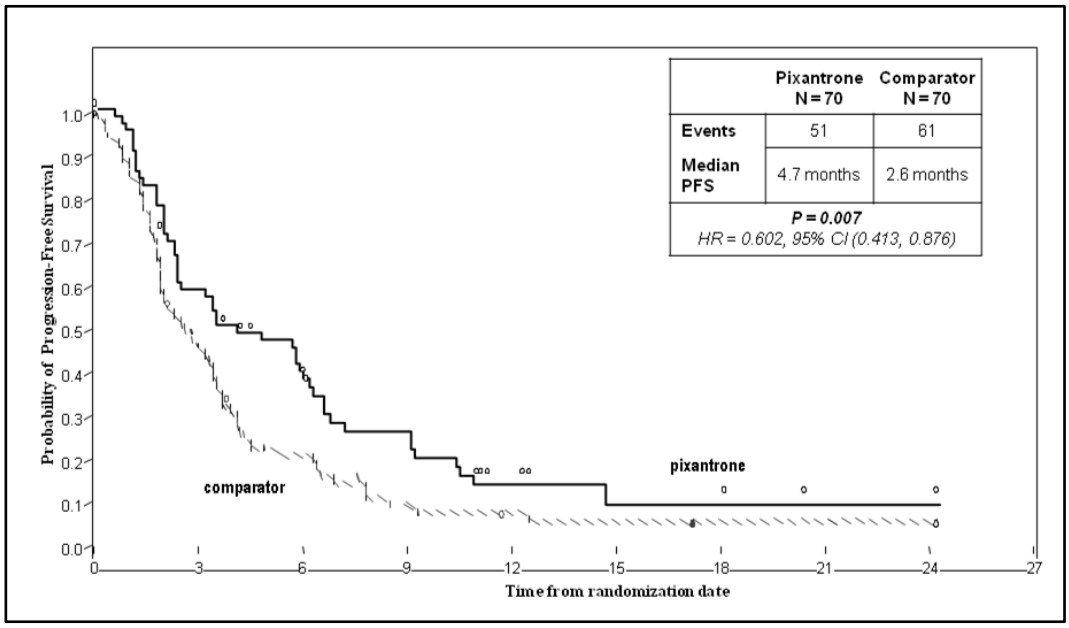
Data Cutoff 30 Sept 2008



3.9.4.3 *Progression-Free Survival*

As a secondary endpoint, PFS was planned to be evaluated at the end-of-treatment and follow-up period as well. By the end of the treatment period (Figure 23), there was a 40% improvement in progression-free-survival for patients who received pixantrone treatment compared to patients receiving comparator treatment (HR=0.60, log rank p-value=0.007). Median PFS was 4.7 months for the pixantrone treatment group and 2.6 months for comparators

Figure 23 Kaplan-Meier Curve of Progression-Free Survival by IAP (ITT Population)
Data Cutoff 30 Sep 2008

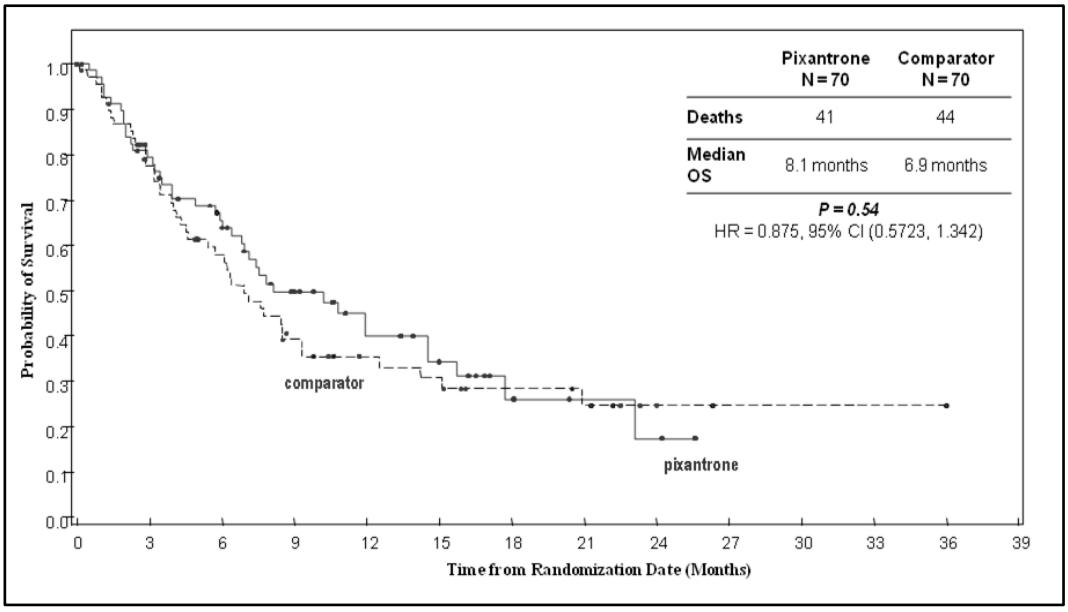


3.9.5 Overall Survival

The final overall survival analysis was planned by the end of study (end of 18 month follow-up period). As shown in Figure 24, at the time of the NDA database cutoff (30 Sept 2008), there were 85 deaths. Median OS for pixantrone treatment was 8.1 months compared to 6.9 months for the comparator treatment. There was a 12% improvement in overall survival that was not statistically significant (HR=0.88, p value=0.54).

Figure 24 Overall Survival by IAP (ITT Population)

Data Cutoff 30 Sep 2008



3.9.6 Prespecified Supportive Analyses

3.9.6.1 *Comparison of Complete Response Rates*

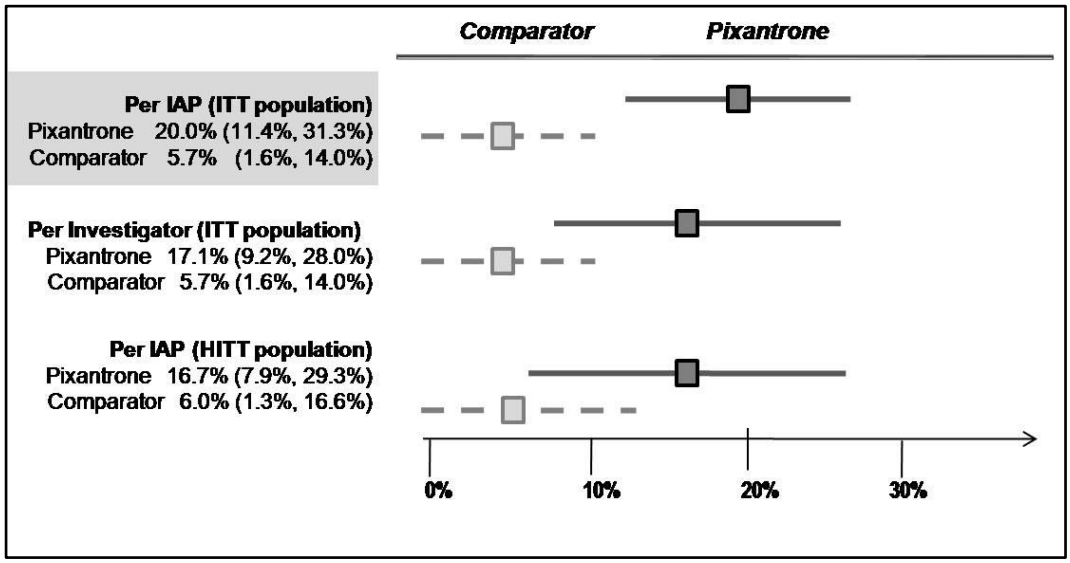
To evaluate the robustness of the primary endpoint, CR/CRu rates were analyzed as follows:

- CR/CRu assessed by IAP in ITT population (primary efficacy endpoint)
- CR/CRu assessed by Investigator in ITT population
- CR/CRu assessed by IAP in HITT population

As displayed in Figure 25, these secondary analyses were consistent with the primary analysis based on IAP assessment in ITT population.

Figure 25 Comparison of Complete Response Rates

Data Cutoff 30 Sep 2008



3.9.6.2 *Comparison of ORR*

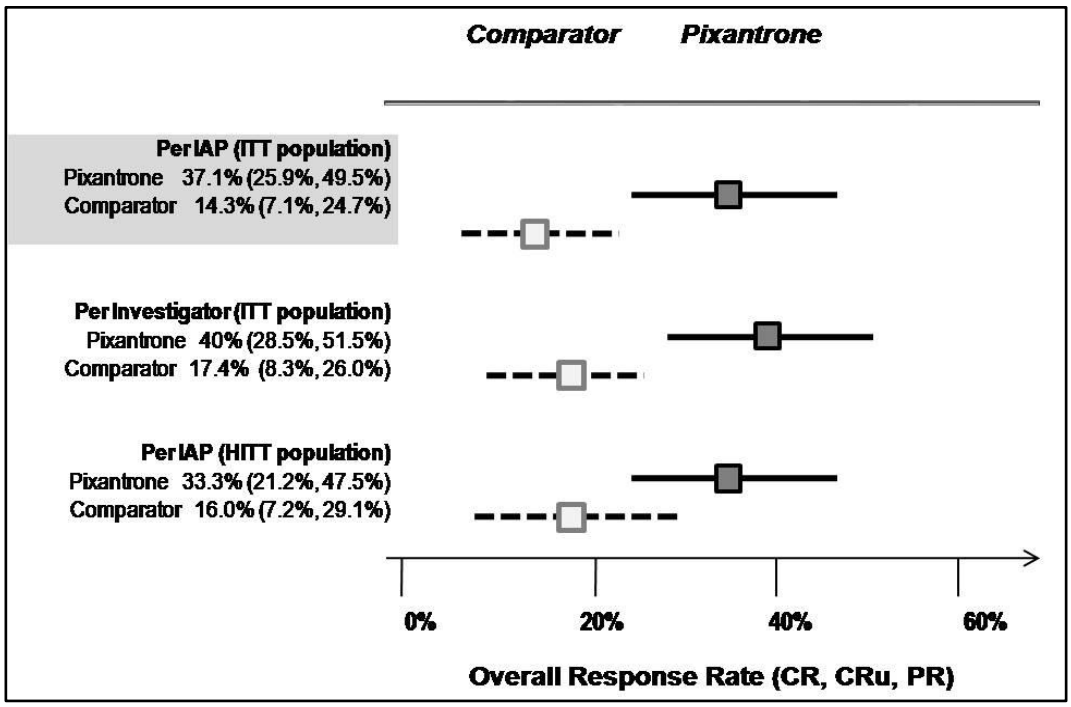
To evaluate the robustness of the secondary endpoint, ORR was also analyzed as follows:

- ORR assessed by IAP in ITT population
- ORR assessed by Investigator in ITT population
- ORR assessed by IAP in HITT population

For all these analyses, ORR demonstrated significant improvement for patients who received pixantrone treatment (Figure 26).

Figure 26 Comparison of ORR

Data Cutoff 30 Sep 2008



3.9.6.3 *Comparison of PFS*

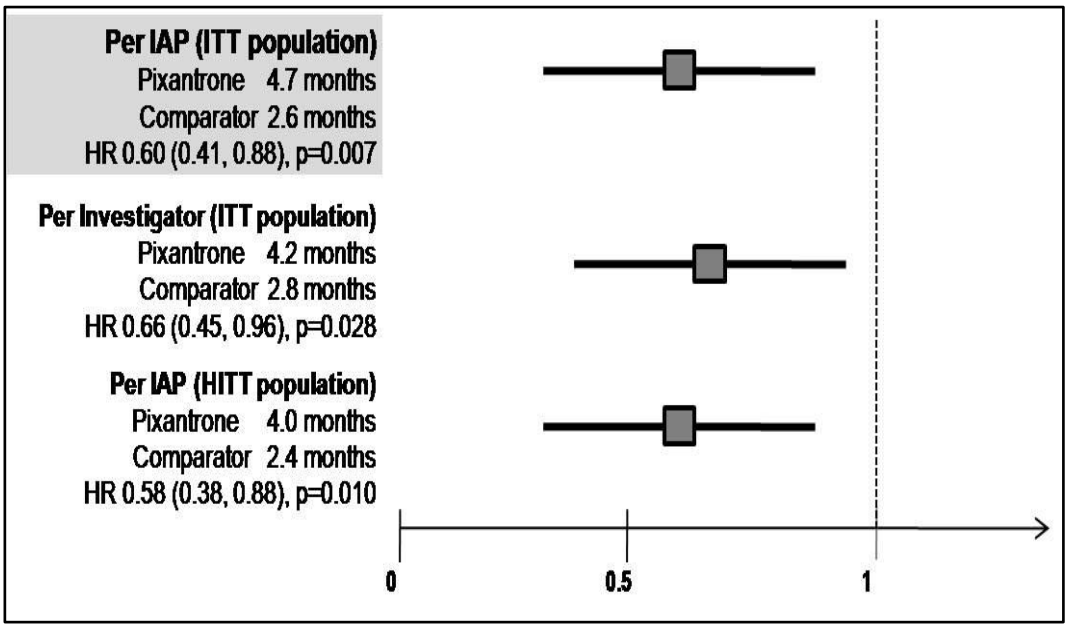
To evaluate the robustness of the secondary endpoint, PFS was also analyzed as follows:

- PFS assessed by IAP in ITT population
- PFS assessed by Investigator in ITT population
- PFS assessed by IAP in HITT population

As shown in Figure 27, in all these analyses, PFS was significantly improved for patients randomized to pixantrone compared to patients randomized to comparator treatment.

Figure 27 Comparison of Hazard Ratios of PFS

Data Cutoff 30 Sep 2008



3.9.6.4 *Planned Subgroup Analyses*

To further explore treatment effects on major demographics and baseline disease characteristics, subgroup analyses were performed on age category (< 65, ≥ 65), gender, race, geographic region, IPI score, status of lymphoma, prior stem cell transplant, and prior rituximab (anti CD20) therapy. Due to the limited sample sizes and exploratory nature, subgroup analyses results should be interpreted cautiously.

3.9.6.5 *Tumor Response in Subgroups*

Table 10 summarizes subgroup analyses on CR/CRu and ORR. CR/CRu and ORR rates were consistently higher in the pixantrone group across the 3 major demographic subgroups, and rates were similar to those seen in the overall study population.

Table 10 Response Rates (n, %) per IAP by Subgroups (ITT Population)
Data Cutoff 30 Sep 2008

Subgroup	Pixantrone		Comparator	
	CR/CRu	ORR	CR/CRu	ORR
Age				
< 65 yr	8/47 (17.0%)	15/47 (31.9%)	4/52 (7.7%)	9/52 (17.3%)
≥ 65 yr	6/23 (26.1%)	11/23 (47.8%)	0/18 (0%)	1/18 (5.6%)
Gender				
Male	8/46 (17.4%)	13/46 (28.3%)	3/40 (7.5%)	6/40 (15.0%)
Female	6/24 (25.0%)	13/24 (54.2%)	1/30 (3.3%)	4/30 (13.3%)
Race				
Caucasian	6/46 (13.0%)	16/46 (34.8%)	2/44 (4.5%)	5/44 (11.4%)
Non-Caucasian	8/24 (33.3%)	10/24 (41.7%)	2/26 (7.7%)	5/26 (19.2%)
Geographic Region				
North America	0/4 (0%)	2/4 (50.0%)	0/4 (0%)	0/4 (0%)
Western Europe	1/19 (5.3%)	3/19 (15.8%)	0/19 (0%)	3/19 (15.8%)
Rest of World[1]	13/47 (27.7%)	21/47 (44.7%)	4/47 (8.5%)	7/47 (14.9%)
IPI Score				
0-1	5/20 (25.0%)	10/20 (50.0%)	1/19 (5.3%)	2/19 (10.5%)
≥ 2	9/50 (18.0%)	16/50 (32.0%)	3/51 (5.9%)	8/51 (15.7%)
Status of Lymphoma				
Refractory Disease	6/40 (15.0%)	12/40 (30.0%)	2/40 (5.0%)	5/40 (12.5%)
Relapse Disease	8/28 (28.6%)	14/28 (50.0%)	2/30 (6.7%)	5/30 (16.7%)
Prior Stem Cell Transplant				
No	13/58 (22.4%)	24/58 (41.4%)	3/60 (5.0%)	7/60 (11.7%)
Yes	1/12 (8.3%)	2/12 (16.7%)	1/10 (10.0%)	3/10 (30.0%)
Prior Anti-CD20 Therapy[1]				
No	8/32 (25.0%)	14/32 (43.8%)	1/31 (3.2%)	3/31 (9.7%)
Yes	6/38 (15.8%)	12/38 (31.6%)	3/39 (7.7%)	7/39 (17.9%)

Source: ISE Appendix Tables 1.1 - 1.10
[1] Rituximab or ibritumomab tiuxetan.

Distribution of IAP-assessed responses (CR, CRu, PR) by was retrospectively analyzed, as shown in Table 11. Major objective responses with pixantrone were observed in all histologic subtypes except the one patient with anaplastic large cell.

CR/CRu and ORR rates were also higher in the pixantrone group than the comparator group

whether the IPI score was < 2 or ≥ 2, or the lymphoma was classified as refractory or relapse. In patients who did not have a prior stem cell transplant, more patients in the pixantrone group than in the comparator group achieved a CR/CRu (22% vs 5%), and the ORR was similarly higher for patients treated with pixantrone (41% vs 12%). There were too few patients (12 pixantrone and 10 comparator patients) who had received prior stem cell transplants to make any meaningful comparisons in this subgroup.

In the DLBCL population, prior anti-CD20 therapy (rituximab or ibritumomab) had little effect on the response rate.

Table 11 Summary of Response Rates per IAP Assessment by Prior Rituximab Treatment (ITT population)

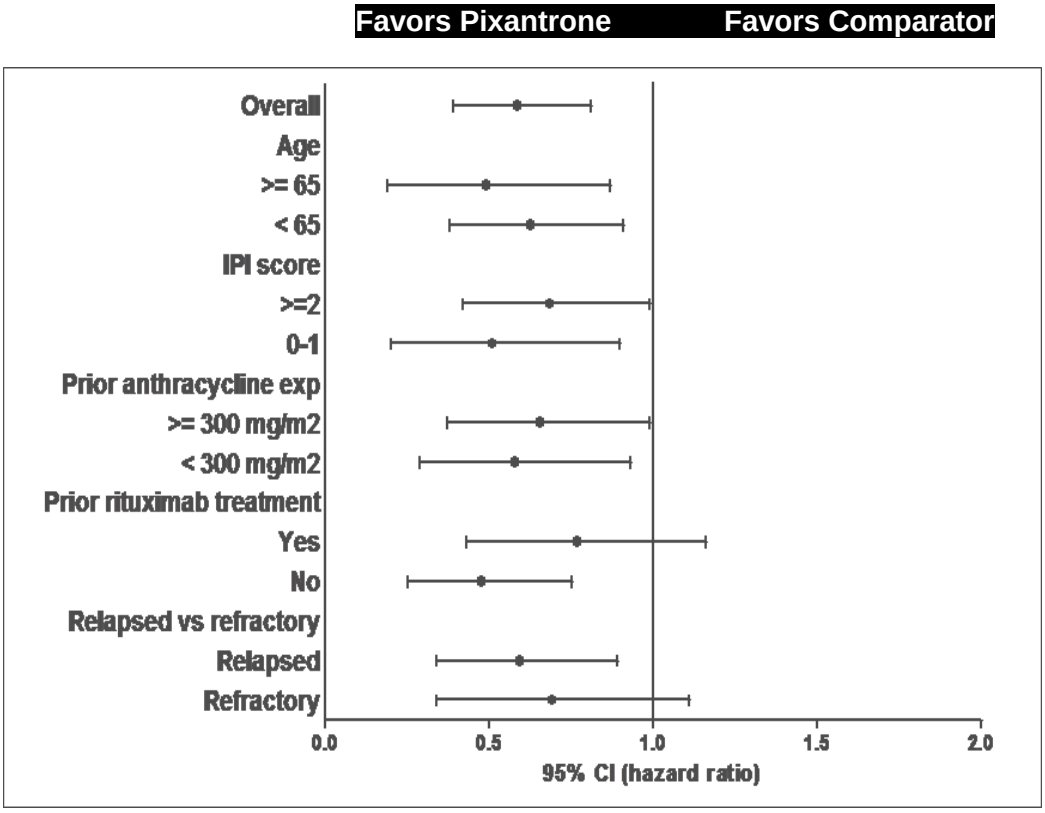
	Pixantrone Group		Comparator Group	
	Prior anti-CD20 Treatment (n=37)	No Prior CD20 Treatment (N=33)	Prior Rituximab Treatment (n=37)	No Prior Rituximab Treatment (N=33)
CR	6 (16.2%)	5 (15.2%)		
CRu	1 (2.7%)	6 (18.2%)	4 (10.3%)	1 (3.2%)
PR	5 (13.5%)	5 (15.2%)	3 (7.7%)	2 (6.5%)
CR/CRu	7 (18.9%)	11 (33.3%)	4 (10.3%)	1 (3.2%)
ORR (CR/CRu/PR)	12 (32.4%)	16 (48.5%)	7 (17.9%)	3 (9.7%)
Source: t_resp_iap_rituximab.rtf				

3.9.7 PFS in Subgroups

As shown in Figure 28, there was a consistent improvement of PFS across all subgroups in patients who received pixantrone treatment compared to patients who received comparator treatment.

Figure 28 Progression-Free Survival by Subgroups

Data Cutoff 30 Sep 2008



3.10 Updated Efficacy Results (Data Cutoff 25 June 2009)

At the time of the 120-Day Safety Update, updated efficacy data was also provided to the FDA. This updated efficacy data included both treatment period and minimum 9 month follow- up data with data cutoff as of 25 June 09. Updated tumor response, CR/CRu, ORR, PFS, and OS are summarized below as supportive analyses.

Of the 140 patients randomized in PIX301, 95 (68%) entered the follow-up period. As of 25 June 2009, 18 patients had completed 18 months of study follow-up (7 in pixantrone and 11 in comparator groups) and 8 patients, all in the pixantrone group, were still ongoing (Table 12).

Table 12 Patient Disposition during Follow-up Period, n (%)

Data Cutoff 25 June 2009

	Pixantrone N=70	Comparator N=70
Entered Follow-Up (FU) Period	52 (74.3%)	43 (61.4%)
Completed 18 months of Follow-Up	7 (13.5%)	11 (25.6%)
Ongoing	8 (15.4%)	0
Died During Follow-Up	30 (57.7%)	26 (60.5%)
Patient Withdrew Consent	3 (5.8%)	5 (11.6%)
Other/Not Verified	4 (7.7%)	1 (2.3%)
Total Number of Deaths[4]	44/70 (62.9%)	47/70 (67.1%)
Source: Table 2 of 120-Day Safety Update		

3.10.1 Tumor Response

Tumor assessments were performed every 8 weeks (+/1 week) through EOT then at the same frequency until 18 months of follow-up had been completed unless a patient progressed or died. Three (3) additional patients in the pixantrone group achieved a CR and 1 patient in the comparator group achieved a CRu, with 2 additional patients in the pixantrone group achieving a PR. All patients improved their response without additional NHL-directed therapy. The updated CR/CRu rate by IAP assessment is 24% (17/70) in the pixantrone group versus 7% (5/70) in the comparator group (*P*=0.005) (Table 13). Eleven patients (16%) treated with pixantrone achieved a CR, but no patients receiving comparator treatment have achieved a CR.

ORR increased to 40% (28/70) in the pixantrone group versus 14% (10/70) in the comparator group (*P*=0.001) (Table 14).

Table 13 CR or CRu by IAP (ITT Population)

Data Cutoff 25 June 2009

	Pixantrone (N=70)	Comparator (N=70)	P-value
CR/CRu, n (%)	17 (24.3%)	5 (7.1%)	*0.005*
95% CI	(15.1%, 36.5%)	(2.4%, 15.9%)	
CR, n (%)	11 (15.7%)	0 (0.0%)	*< 0.001*
95% CI	(8.2%, 26.7%)	(0.0%, 5.1%)	
CRu, n (%)	6 (8.6%)	5 (7.1%)	*0.764*
95% CI	(3.3%, 18.0%)	(2.4%, 15.9%)	
Source: t_resp_cr_ucr_iap_itt.rtf / P-value by Fisher exact test.			

Figure 29 shows duration of CR/CRu by individual patients.

Figure 29 Duration of CR/CRu by Patient – IAP Assessment (ITT population)

Data Cutoff 25 June 2009

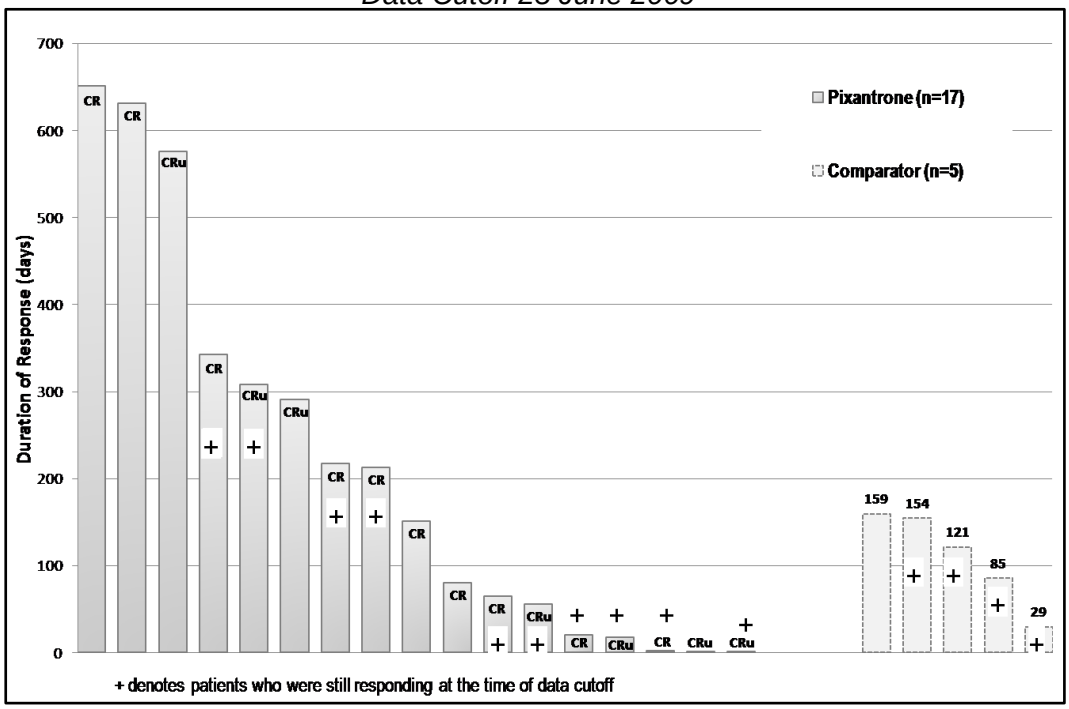


Table 14 ORR (CR, CRu, PR) by IAP (ITT Population)

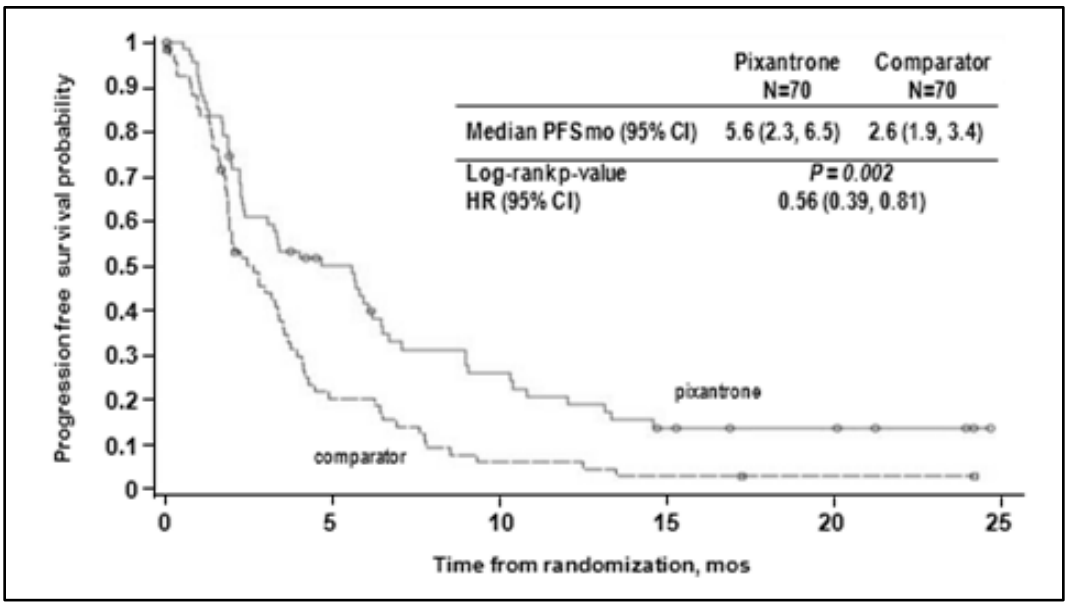
Data Cutoff 25 June 2009

	Pixantrone (N=70)	**Comparator (N=70)**	**P-value**
ORR, n (%)	28 (40.0%)	10 (14.3%)	*0.001*
95% CI	(28.5%, 52.4%)	(7.1%, 24.7%)	
Source: 120-Day Report Table 3.5.1 P-value by Fisher exact test.			

The updated data (Figure 30) continues to support the superior efficacy of pixantrone over comparator, demonstrating a 44% improvement in pixantrone treatment with median PFS of 5.6 months for pixantrone treatment versus 2.6 months for the comparator group (HR=0.56; *P=0.002)*.

Figure 30 Kaplan-Meier Curve of PFS by IAP (ITT population)

Data Cutoff 25 June 2009

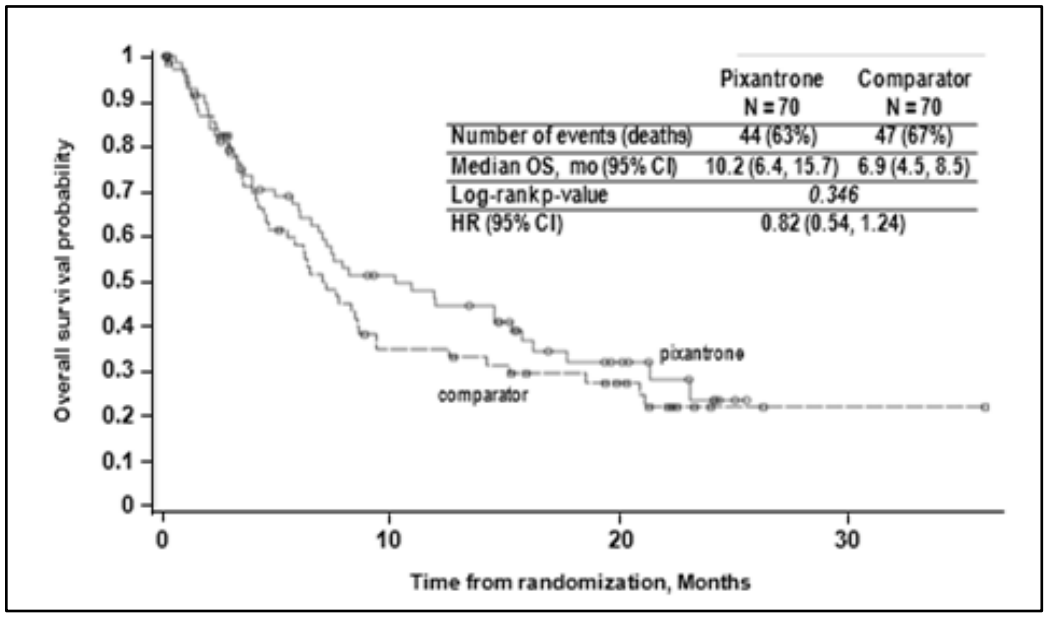


Source: 120 Day Report, Table 8 and Figure 1

Median overall survival increased to 10.2 months for the pixantrone group compared to 6.9 months for the comparator group (HR 0.82, p=0.346). At 12 months, 21% of patients in the pixantrone group, compared to 8% in the comparator group, were alive without disease progression (Figure 31).

Figure 31 Kaplan-Meier Curve of Overall Survival by IAP (ITT population)

Data Cutoff 25 June 2009



Source: 120-Day Report, Figure 3.3.1, Table 3.3.1

3.11 Overall Efficacy Conclusions

The effectiveness of pixantrone has been demonstrated in a randomized, multicenter, multinational, single-agent well-controlled, phase 3 study. Study PIX301 was designed to evaluate the efficacy and safety of pixantrone given as a single agent at 85 mg/m^2 by IV infusion on days 1, 8, and 15 of 28-day cycles for up to 6 cycles. The study enrolled 140 patients with relapsed or refractory aggressive non-Hodgkin's lymphoma (NHL) who had received at least two prior lines of therapy.

These heavily pretreated patients with relapsed and refractory NHL who received pixantrone achieved superior efficacy and clinical benefit compared with patients randomized to other single-agent chemotherapeutic agents as measured by the following (data cutoff 30 September 2008):

- Significantly higher CR/CRu rate (20% vs 6%, p=0.021)
  - 11.4% CRs in the pixantrone group versus 0% in the comparator group
- Significantly higher ORR (37% vs 14%,p= 0.003)
- Significant improvement in PFS (median 4.7 vs 2.6 months, HR= 0.60, p=0.007)

- Longer median duration of the CR/CRu responses (7.0 months vs 3.4 months, HR=0.25, p=0.033)

Results from the follow-up period reinforced conclusions from the study period. As of the Safety Update data cutoff (25 June 2009), three additional pixantrone patients achieved a CR and one additional patient achieved a PR. Only one patient in the comparator group displayed a response improvement during follow-up, converting from a PR to CRu. The updated CR/CRu rate is 24% in the pixantrone group versus 7% in the comparator group (*P*=0.005), with 16% CR rate on the pixantrone arm versus 0 responses on the comparator arm.

As shown in

Figure 30, with maturation of the follow-up data, the PFS between the groups has widened to a median of 5.6 versus 2.6 months *(*HR = 0.56, p=0.002). Survival data continue to be collected in the follow-up phase of the study; the data currently show an 18% reduction in mortality rate and a 3.3 month advantage for the pixantrone group (median 10.2 vs 6.9 months, HR=0.82, p=0.346).

4 SAFETY OF PIXANTRONE

A Data Monitoring Committee (DMC) evaluated safety data throughout the PIX301 study according to their charter. The DMC, which operated independently of CTI and investigators, consisted of 3 voting members: a biostatistician, an oncologist, and a cardiologist specializing in cardiac effects of oncologic drugs. The primary goal of the DMC was to assure that the study proceeded in an ethical manner with a reasonable balance between risk and benefit.

4.1 Studies included in Safety Assessment

Table 15 summarizes the clinical experience with pixantrone, which includes 348 patients who have received at least one dose of pixantrone either as a single-agent or as a part of combination therapy, as well as patients in the phase 3 study (PIX301).

Table 15 Subjects Exposed to Pixantrone across All Studies in the Clinical Development Program

Summary Group	Indication	Study	Study Pixantrone Doses (mg/m^2)	N
Controlled Single Agent Therapy	NHL	**PIX301**	85	68
Uncontrolled Single Agent Therapy	NHL	AZA I-03 AZA II-01	5.0-84.0 85	59
	Other Malignancies[1]	AZA I-01 AZA I-02 AZA I-04 PIX 109	20-240 5.0-112.5 180, 270 80-110	70
Combination Therapy[2]	NHL	AZA I-05 AZA I-06 AZA I-07 AZA II-02 AZA III-02	80 80-120 80-180 80 90	151
Total Exposed to Pixantrone				**348**

[1] Other malignancies included solid tumors and acute refractory myelogenous leukemia
Source: PIX301 ISS Table 1-3
[2] Pixantrone was administered in combination with a range of antitumor drugs including cyclophosphamide, vincristine, prednisone, cytarabine, methylprednisolone, cisplatin, and rituximab. see Appendix 4 for the combinations tested in each of the studies.

The primary safety analysis of pixantrone is based on data from the controlled single-agent study, PIX301. In that study, safety data for 68 patients who received at least one dose of pixantrone were directly compared to safety data from 67 patients who received a comparator single-agent drug. (Two patients in the pixantrone group and 3 patients in the comparator group discontinued the study prior to receiving the first dose of study drug.)

Pixantrone was given at a dose of 85 mg/m^2 on days 1, 8, and 15 of each 28-day cycle for up to 6 cycles. Therapy used in the comparator group was the investigator's choice of oxaliplatin, ifosfamide, vinorelbine, etoposide, mitoxantrone, gemcitabine; rituximab (CD20+ patients only) as described in 3.3.1.

4.2 Exposure Summary

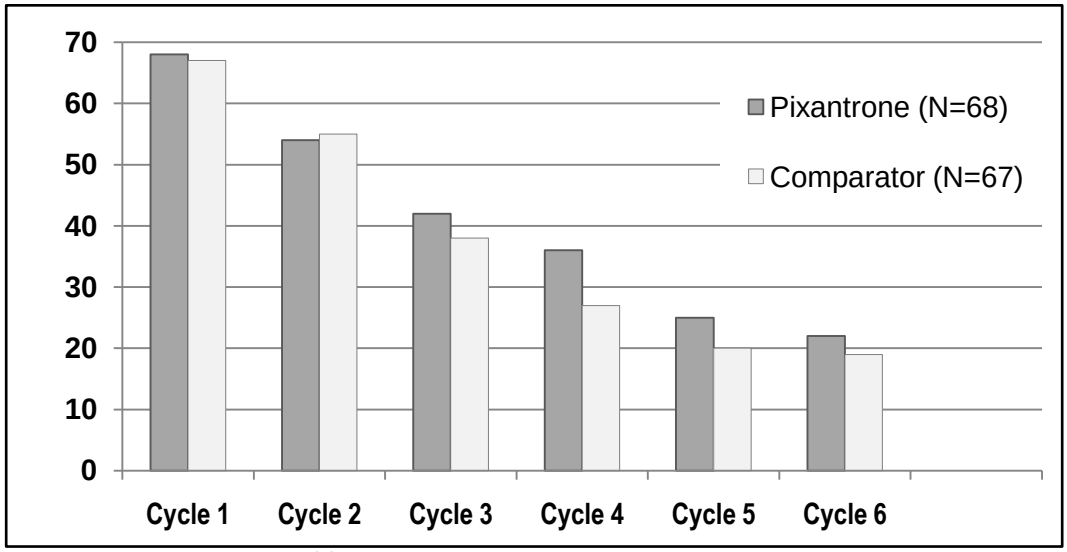
4.2.1 Overall Exposure

Pixantrone cycles were 28 days; comparator cycle durations were 21 days for oxaliplatin and mitoxantrone and 28 days for all other drugs. The median number of treatment cycles given

was 4 for the pixantrone group and 3 for the comparator agent group (Figure 32). More patients received all 6 cycles of study treatment in the pixantrone group (32%) than in the comparator group (28%), and more patients in the pixantrone group received ≥ 4 cycles of therapy (53%) than in the comparator group (40%).

Figure 32 Cumulative % of Patients Receiving Treatment Cycles (safety population)

Data Cutoff 30 Sep 2008



Source: PIX301 CSR Table 14.3.0.1

4.2.2 Dose Intensity, Modifications and Interruption

The primary reason for dose reductions in both arms was hematologic toxicity. A summary of pixantrone dose intensity is provided in Table 16. The primary reason for dose reductions in both arms was hematologic toxicity.

These dose intensity analyses demonstrate that the dose and schedule utilized in this trial were appropriate.

Table 16 Summary of Pixantrone Dose Intensity (N=68)

Data Cutoff 30 Sep 2008

	Actual Dose Intensity mg/m^2/week	**Relative Dose Intensity % Accounting for Missed Doses**
Median (range)	55.0 (24-64)	90.6 (20-102)
Source: PIX301 CSR Table 14.3.0.3 The formula for relative dose intensity, accounting for doses missed, is the total dose received (mg/m^2) divided by 3*85 mg/m^2*number of cycles). The relative dose intensity calculation in the CSR did not take into account missed doses.		

Adverse events leading to withdrawal are provided later in Table 19. As shown in Table 17, only 2.9% of patients in the pixantrone group missed doses and 17.6% had dose reductions. The criteria for dose modification in the PIX301 protocol are provided in Appendix 3.

Table 17 Dose Reductions and Missed Doses (Safety Population)

Data Cutoff 30 Sep 2008

	Pixantrone (N=68)	**Comparator (N=67)**
Patients with Doses Missed, n (%)	2 (2.9)	0
Patients with Dose Reductions, n (%)	12 (17.6)	10 (14.9)
Source: PIX301 CSR Table 14.3.0.4		

4.3 PIX301 Safety Data

Safety assessments included adverse events, clinical hematology and chemistry laboratory measurements, electrocardiograms (ECGs), cardiac function as assessed by MUGA and/or echocardiography, and physical examinations throughout the study treatment period. All patients were scheduled to have evaluation of LVEF 6 months after the end-of-treatment (off-treatment) visit.

4.3.1 Adverse Events

Adverse events in PIX301 were consistent with expected events in heavily pretreated NHL patients. More than 90% of all patients in PIX301 experienced at least one AE. Table 18 shows treatment-emergent adverse events (all grades and grade 3/4) that occurred in ≥ 5% of patients.

Table 18 Number (%) of Patients with Adverse Events Occurring in ≥ 5% of Patients in Either Group (Safety Population)

System Organ Class MedDRA Preferred Term	**Pixantrone (N=68)**		**Comparator (N=67)**	
	All grades	Grade 3/4	All grades	Grade 3/4
Patients with Any AE	**66 (97.1)**	**39 (57.4)**	**58 (86.6)**	**22 (32.8)**
Blood & Lymphatic Disorders	**50 (73.5)**	**37 (54.4)**	**34 (50.7)**	**24 (35.8)**
Neutropenia	34 (50.0)	28 (41.2)	16 (23.9)	13 (19.4)
Anemia	20 (29.4)	4 (5.9)	22 (32.8)	9 (13.4)
Leukopenia	17 (25.0)	16 (23.5)	5 (7.5)	3 (4.5)
Thrombocytopenia	14 (20.6)	8 (11.8)	13 (19.4)	7 (10.4)
Febrile neutropenia	6 (8.8)	5 (7.4)	2 (3.0)	2 (3.0)
Gastrointestinal Disorders	**33 (48.5)**	**9 (13.2)**	**26 (38.8)**	**7 (10.4)**
Nausea	12 (17.6)	0	10 (14.9)	1 (1.5)
Abdominal pain	10 (14.7)	5 (7.4)	6 (9.0)	3 (4.5)
Constipation	7 (10.3)	0	3 (4.5)	0
Vomiting	4 (5.9)	0	10 (14.9)	2 (3.0)
General Disorders & Administration Site Conditions	**40 (58.8)**	**7 (10.3)**	**30 (44.8)**	**11 (16.4)**
Asthenia	15 (22.1)	3 (4.4)	9 (13.4)	3 (4.5)
Pyrexia	15 (22.1)	3 (4.4)	16 (23.9)	6 (9.0)
Oedema peripheral	10 (14.7)	0	4 (6.0)	0
Fatigue	8 (11.8)	1 (1.5)	9 (13.4)	0
Mucosal inflammation	7 (10.3)	0	2 (3.0)	1 (1.5)
Infections & Infestations	**29 (42.6)**	**12 (17.6)**	**18 (26.9)**	**9 (13.4)**
Pneumonia	5 (7.4)	4 (5.9)	4 (6.0)	3 (4.5)
Cellulitis	4 (5.9)	2 (2.9)	2 (3.0)	2 (3.0)
Bronchitis	4 (5.9)	1 (1.5)	0	0

Table 18 Number (%) of Patients with Adverse Events Occurring in ≥ 5% of Patients in Either Group (Safety Population)

System Organ Class MedDRA Preferred Term	Pixantrone (N=68)		Comparator (N=67)	
	All grades	Grade 3/4	All grades	Grade 3/4
Investigations	**22 (32.4)**	**8 (11.8)**	**19 (28.4)**	**6 (9.0)**
Ejection fraction decreased	13 (19.1)	1 (1.5)	7 (10.4)	0
Weight decreased	5 (7.4)	1 (1.5)	5 (7.5)	1 (1.5)
Platelet count decreased	4 (5.9)	2 (2.9)	2 (3.0)	2 (3.0)
Metabolism & Nutrition Disorders	**21 (30.9)**	**9 (13.2)**	**14 (20.9)**	**4 (6.0)**
Anorexia	8 (11.8)	2 (2.9)	4 (6.0)	0
Dehydration	5 (7.4)	3 (4.4)	2 (3.0)	0
Musculoskeletal & Connective Tissue Disorders	**12 (17.6)**	**0**	**9 (13.4)**	**2 (3.0)**
Pain in extremity	5 (7.4)	0	2 (3.0)	1 (1.5)
Back pain	5 (7.4)	0	2 (3.0)	0
Renal & Urinary Disorders	**10 (14.7)**	**1 (1.5)**	**5 (7.5)**	**3 (4.5)**
Chromaturia	4 (5.9)	0	0	0
Renal failure	0	0	5 (7.5)	3 (4.5)
Respiratory, Thoracic & Mediastinal Disorders	**29 (42.6)**	**3 (4.4)**	**14 (20.9)**	**5 (7.5)**
Cough	15 (22.1)	0	3 (4.5)	0
Dyspnea	9 (13.2)	4 (5.9)	8 (11.9)	3 (4.5)
Rhinorrhea	4 (5.9)	0	0	0
Pleural effusion	3 (4.4)	1 (1.5)	4 (6.0)	1 (1.5)
Skin & Subcutaneous Tissue Disorders	**19 (27.9)**	**2 (2.9)**	**13 (19.4)**	**0**
Alopecia	9 (13.2)	0	2 (3.0)	0
Skin discoloration	6 (8.8)	0	0	0
Vascular Disorders	**6 (8.8)**	**2 (2.9)**	**8 (11.9)**	**3 (4.5)**
Hypotension	5 (7.4)	2 (2.9)	3 (4.5)	1 (1.5)

Source: PIX301 CSR Table 14.3.1.1

The most commonly reported (>20% of patients) adverse events of all severities during the

study in the pixantrone group versus the comparator group were neutropenia (50% vs 24%), anemia (29% vs 33%), leukopenia (25% vs 8%), pyrexia (22% vs 24%), asthenia (22% vs 13%), cough (22% vs 5%), and thrombocytopenia (21% vs 19%). However, most of these events were grade 1 or 2 in severity.

Grade 3/4 adverse events that occurred at a higher frequency in the pixantrone group than the comparator group were neutropenia (41% vs 19%) and leukopenia (24% vs 5%). The rate of grade 3/4 febrile neutropenia was low in both treatment groups, 7% and 3%, respectively.

Despite the higher incidence of grade 3/4 neutropenia in pixantrone patients, the rates of severe (grade 3/4) infections were similar between treatment groups. It should be noted that the time at risk for on study adverse events was longer for the pixantrone arm due to the 3-week cycle duration for oxaliplatin and mitoxantrone (34 patients, 49%) and a higher median number of cycles (4 versus 3).

4.3.2 Adverse Events That Led to Study Treatment Withdrawal

The frequency of adverse events resulting in study drug discontinuation was similar in both treatment groups (Table 19): 25 patients (37%) in the pixantrone group and 23 patients (34%) in the comparator group.

More patients in the pixantrone group discontinued for adverse events of neutropenia, asthenia, and ejection fraction decrease, whereas discontinuation for adverse events of thrombocytopenia, anemia, lymphadenopathy, decreased platelet count and renal failure occurred only in the comparator group. Malignant neoplasm progression was the AE used to describe discontinuation of study treatment for 6 (9%) patients in the comparator group compared to no (0%) patients in the pixantrone group.

Table 19 Number (%) of Patients with Adverse Events of Any Grade Leading to Study Treatment Withdrawal Occurring in ≥ 2% of Patients in Either Treatment Group

	Pixantrone (N=68)	Comparator (N=67)
Any Adverse Event Leading to Withdrawal[1]	25 (36.8)	23 (34.3)
Neutropenia	4 (5.9)	0
Asthenia	3 (4.4)	0
Leukopenia	2 (2.9)	1 (1.5)
Cardiac failure	2 (2.9)	1 (1.5)
Pyrexia	2 (2.9)	1 (1.5)
Ejection fraction decreased	2 (2.9)	0
Pleural effusion	1 (1.5)	3 (4.5)
Pneumonia	1 (1.5)	2 (3.0)
Dyspnea	1 (1.5)	2 (3.0)
Respiratory failure	1 (1.5)	2 (3.0)
Malignant neoplasm progression	0	6 (9.0)
Thrombocytopenia	0	3 (4.5)
Anemia	0	2 (3.0)
Lymphadenopathy	0	2 (3.0)
Platelet count decreased	0	2 (3.0)
Renal failure	0	2 (3.0)

Source: PIX301 CSR Table 14.3.1.7
[1] The percentage of patients includes all patients who discontinued study treatment due to an AE, including those who discontinued due to disease progression.

4.3.3 Serious Adverse Events

Thirty-five patients (52%) in the pixantrone treatment group and 30 patients (45%) in the comparator group had serious adverse events. The most frequent SAEs in both treatment groups were neutropenia and pyrexia (Table 20). The only SAE that occurred significantly more often in one treatment group was malignant neoplasm progression, which was more frequent in the comparator group (2% vs 13%, $P = 0.009$).

Table 20 Number (%) of Patients with Serious Adverse Events Occurring in ≥ 2% of Patients in Either Treatment Group (Safety Population)

	Pixantrone (N=68)	Comparator (N=67)
Any Serious Adverse Event	35 (51.5)	30 (44.8)
Neutropenia	9 (13.2)	6 (9.0)
Pyrexia	7 (10.3)	7 (10.4)
Pneumonia	5 (7.4)	4 (6.0)
Febrile neutropenia	4 (5.9)	2 (3.0)
Leukopenia	4 (5.9)	2 (3.0)
Abdominal pain	3 (4.4)	3 (4.5)
Dyspnea	3 (4.4)	2 (3.0)
Hypotension	3 (4.4)	2 (3.0)
Anemia	2 (2.9)	5 (7.5)
Respiratory failure	2 (2.9)	2 (3.0)
Cellulitis	2 (2.9)	2 (3.0)
Cardiac failure	2 (2.9)	1 (1.5)
Dehydration	2 (2.9)	1 (1.5)
Cardiac failure congestive	2 (2.9)	0
Septic shock	2 (2.9)	0
Bronchitis	2 (2.9)	0
Pneumonitis	2 (2.9)	0
Malignant neoplasm progression	1 (1.5)	9 (13.4)
Thrombocytopenia	1 (1.5)	6 (9.0)
Pleural effusion	1 (1.5)	2 (3.0)
Renal failure	0	4 (6.0)
Vomiting	0	2 (3.0)

Source: PIX301 CSR Table 14.3.1.5

4.3.4 Deaths

An in-depth review of deaths that occurred during PIX301 identified no concerning trends in adverse event patterns. Twenty-two patients died within 30 days of their last dose of study treatment: 10 patients in the pixantrone group and 12 patients in the comparator group. The majority of those deaths were related to the underlying NHL (Table 21). One death in the pixantrone group, patient #079 who died of septic shock, was considered related to study drug.

Table 21 Deaths that Occurred ≤ 30 Days after the Last Dose of Study Drug

Pt ID Age/Sex	Cause of death	AE (preferred term) resulting in Death	Related (per Invest-igator)	First Dose Date	Last Dose Date	Days from Last Dose to Death
Pixantrone Group						
#015 68/M	Likely Heart Failure	Cardiac failure Hypotension	No	5-Jul-05	(b) (6)	24
#018 60/M	(Progressive) NHL	Malignant neoplasm progression	No	31-Aug-05	(b) (6)	17
#050 45/F	NHL	Non-Hodgkin's lymphoma	No	01-Jun-06	(b) (6)	22
#076 55/M	Progressive Disease	Acute respiratory distress syndrome	No	17-Oct-06	(b) (6)	5
#079 29/F	Septic Shock	Septic shock	Yes	02-Nov-06	(b) (6)	8
#085 49/M	Respiratory obstruction with progressive disease	Obstructive airways disorder	No	22-Dec-06	(b) (6)	28
#090 51/F	Pulmonary Embolus	Pulmonary venous thrombosis	No	02-Feb-07	(b) (6)	11
#0103 71/F	Disease Progression	Metastases to abdominal cavity	No	14-May-07	(b) (6)	6
#115 74/M	Pneumonia-Sepsis	Pneumonia, sepsis	No	10-Aug-07	(b) (6)	26
#132 73/F	Multiorgan failure and cardiocirculatory arrest	Circulatory collapse, Multiorgan failure	No	21-Dec-07	(b) (6)	25
Comparator Group						
#012 57/F	Heart Failure from progressive disease	Cardiac failure	No	3-Jun-05	(b) (6)	9
#023 51/F	Progressive Disease	Malignant neoplasm progression	No	5-Nov-05	(b) (6)	18
#030 36/M	Progressive Disease	Malignant neoplasm progression	No	23-Dec-05	(b) (6)	24
#031 62/F	Progression of Disease	Malignant neoplasm progression	No	27-Dec-05	(b) (6)	29
#037 38/M	Progressive Disease	Malignant neoplasm progression	No	25-Feb-06	(b) (6)	30
#061 60/F	Disease Progression	Renal failure	No	14-Jul-06	(b) (6)	27

Table 21 Deaths that Occurred ≤ 30 Days after the Last Dose of Study Drug

Pt ID Age/Sex	Cause of death	AE (preferred term) resulting in Death	Related (per Invest-igator)	First Dose Date	Last Dose Date	Days from Last Dose to Death
#067 34/F	Progressive Disease	Pleural effusion, respiratory failure, sepsis	No	05-Sep-06	(b) (6)	26
#092 77/F	Disease Progression	None recorded[+]	No	13-Feb-07	(b) (6)	21
#093 58/F	Neuromeningeal progression of NHL	Malignant neoplasm progression	No	12-Mar-07	(b) (6)	19
#097 47/F	Progressive Disease	Malignant neoplasm progression	No	27-Mar-07	(b) (6)	17
#126 55/M	Pneumonia left side	Pneumonia	No	18-Oct-07	(b) (6)	8
#138 26/F	Progressive Disease	Obstructive airways disorder	No	25-Feb-08	(b) (6)	26

[+]Not reported with an outcome of death in clinical database. SAE with an outcome of death reported to pharmacovigilance.
Source: PIX301 CSR listings 16.2.4.1, 16.2.5.1, 16.2.7.1,16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.7

As of the data cutoff of 25 June 2009, which included data from both the study treatment period and the ongoing follow-up period, 63% (44/70) of patients in the pixantrone group and 67% (47/70) of patients in the comparator group had died. Three deaths that occurred more than 30 days after the last study treatment were considered by the investigator to be related to treatment. In the pixantrone group, patient #035 died of presumptive acute CHF 48 days after the last dose of study drug, and patient #087 died of myelodysplastic syndrome (MDS) 14 months after EOT and following subsequent treatment with several multiple drug regimens including RICE and R-DHAP; see details in section 4.4. Patient #083 in the comparator group died of renal failure 66 days after the last dose of oxaliplatin.

4.3.5 Adverse Events Associated with Anthracycline-Like Agents

The clinical use of anthracycline-like agents is limited by the development of a cumulative dose-related progressive cardiomyopathy that irreversibly evolves toward congestive heart failure. [35] The pathophysiology of anthracycline-induced cardiomyopathy is related to acute and subchronic oxidative injury.[36] The risk for clinical CHF approaches 26% in patients who

receive a lifetime doxorubicin dose > 550 mg/m^2.[37] For this reason, although there are notable differences between pixantrone and doxorubicin (see section 2.2), as patients were enrolled in PIX301 with lifetime anthracycline doxorubicin-equivalent cumulative doses as high as 450 mg/m^2, cardiac adverse events were closely and proactively evaluated.

At baseline, a cardiac history form was completed focusing on past history of heart disease and comorbid conditions that are independent risk factors for anthracycline-induced congestive heart failure.[38] The cardiac history was updated at the end of treatment and at all follow-up assessments.

A higher percentage of patients in the pixantrone group had a baseline history of intrinsic cardiac disorders (coronary artery disease, myocardial infarction, CHF, cardiomyopathy and valvular heart disease) than did comparator patients (Table 22).

Table 22 Patients with Baseline History of Cardiac Risk Factors (ITT population)

	Pixantrone (N=70)	**Comparator** (N=70)
Patients with Any Cardiac History Event	26 (37.1%)	28 (40.0%)
Hypertension	16 (22.9%)	18 (25.7%)
Coronary artery disease	3 (4.3%)	3 (4.3%)
Myocardial infarction	1 (1.4%)	3 (4.3%)
Congestive heart failure	3 (4.3%)	0
Atrial arrhythmia	1 (1.4%)	3 (4.3%)
Ventricular arrhythmia	0	2 (2.9%)
Valvular heart disease	5 (7.1%)	2 (2.9%)
Cardiomyopathy	2 (2.9%)	0
Diabetes	8 (11.4%)	10 (14.3%)
Other	7 (10%)	7 (10**%)**

Source: PIX301 CSR Table 14.1.9

Cardiac left ventricular ejection fraction was assessed every 2 cycles by serial cardiac MUGA scans (or echocardiograms if MUGA was unavailable) for safety surveillance during the trial. In addition, the following events were required to be reported in the same manner as SAEs,

as cardiac events of interest:

- Grade 3 and 4 cardiac events, including those thought by the investigator to be unrelated to study drug
- All LVEF decreases ≥ 10 percentage points from baseline

Cardiac adverse events of interest ≥ grade 3 that occurred in PIX301 are summarized in Table 23. There were 5 (7%) in the pixantrone arm versus one (2%) in the control arm.

Table 23 Number (%) of Patients with ≥ Grade 3 Treatment-Emergent Cardiac Adverse Events of Interest (Safety Population)

	Pixantrone (N=68)	Comparator (N=67)
Patients with at least 1 cardiac adverse event of interest*	5 (7.4%)	1 (1.5%)
Patients with each cardiac adverse event		
Ejection fraction decreased[1]	1 (1.5%)	0
Cardiac failure congestive[2]	2 (2.9%)	0
Cardiac failure[3]	2 (2.9%)	1 (1.5%)

Source: PIX301 CSR Table 14.3.1.8
*Not included is patient #008 (pixantrone) who received 2 doses of pixantrone then was hospitalized for a serious infection and diagnosed with progressive disease before the third dose of cycle 1 could be given; he died of cardiac arrest 46 days later.
[1]Patient #056 (pixantrone)
[2]Patients #035 and #109 (pixantrone)
[3] Patients #004 and #015 (pixantrone) and #012 (comparator).
Patient #015 on the pixantrone arm and patient #012 on the comparator arm also appear in Table 21

Two additional patients had grade ≥ 3 CHF reported in follow-up: patient #087 in the pixantrone group and patient #110 in the comparator group.

The EOT LVEF values decreased by a median of 5 percentage points in pixantrone patients and increased by 1 percentage point in comparator patients compared to baseline values.

At the end of the treatment period in PIX301, doxorubicin equivalent exposure was significantly higher in the pixantrone group than in the comparator group (528 mg/m^2 vs 331 mg/m^2; $p < 0.001$, range 400 mg/m^2 to > 900 mg/m^2). At similar exposure levels, doxorubicin is reported in the literature as associated with an incidence of CHF ranging from 26% to 48% (Swain 2003). In PIX301, CHF occurring during the study treatment period was

infrequent, not considered to be related to study drug in all but one case and, importantly, was not dependent on cumulative exposure. Similarly, all but one of the LVEF declines identified during treatment were grade 1 or 2.

4.3.6 Independent Review of Cardiac Events

After database lock, an independent cardiologist reviewed the study's safety data to provide an overview of cardiac safety and to place any observed events within the perspective of published data on the cardiotoxicity of anthracycline-class drugs.[39] The independent cardiologist reviewed the cardiac events in PIX301 using the cardiotoxicity criteria defined by Swain and colleagues[14] in their retrospective analysis of cardiotoxicity in patients treated with doxorubicin.

All information provided in the PIX301 study report, including the assessment of causality by the investigator, was used to classify potential pixantrone-associated cardiac events. Cases with incomplete or conflicting information were reported as "possible" or "unlikely." Of all cardiac events reported in PIX301 (Table 23), the independent cardiologist identified 2 patients who had possibly or probably pixantrone-associated CHF.

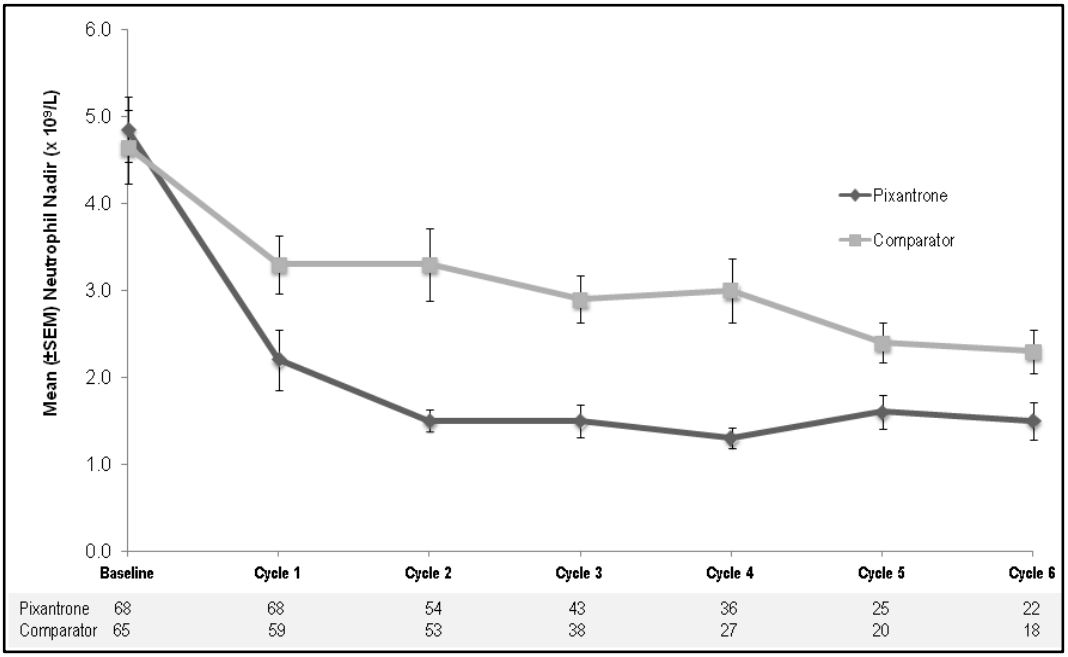
4.3.7 Hematologic Toxicity

Bone marrow suppression manifested by neutropenia is the dose-limiting toxicity of pixantrone. Using the worst post-baseline values during study treatment, leukocyte counts worsened (i.e., a shift of at least one toxicity grade) in 87% of patients in the pixantrone group compared to 54% in the comparator group, with a comparable trend for neutrophils. The majority of those shifts were to grade 1 or 2 toxicity. The shift to grade 3 or 4 leukocyte counts was 35% vs 13%.

Worsening of hemoglobin levels (by worst post-baseline value) occurred in 52% of pixantrone versus 68% of comparator recipients; all of those shifts were to either grade 1 or 2 toxicity, with one hemoglobin shift to grade 3 toxicity in a comparator patient. Those worsening shifts are reflected in the rate of grade 3/4 hematologic adverse events and adverse events associated with treatment withdrawal (shown previously in Table 19).

After an initial decline from baseline to cycle 2, mean neutrophil nadirs remained stable through subsequent cycles (Figure 33).

Figure 33 Mean Neutrophil Nadirs by Cycle and Treatment Arm (Safety Population) *Data Cutoff 30 Sep 2008*



Evidence for the lack of cumulative toxicity is also provided by the 91% median dose intensity delivered for pixantrone patients (Table 16). To achieve this degree of dose intensity, only 52% of patients received granulocyte growth factors (Table 24).

Management of hematologic toxicity is part of standard supportive care for patients receiving cytotoxic cancer therapy. Table 24 summarizes treatment administered to patients for hematologic effects during the study. More patients in the comparator group required erythropoietic stimulants, while neutrophil stimulants were used more frequently in the pixantrone group.

Table 24 Number (%) of Patients Receiving Treatment for Hematologic Toxicity (Safety Population)

	Pixantrone (N=68)	Comparator (N=67)
Immunostimulants (Includes filgrastim, granulocyte colony-stimulating factor, lenograstim, pegfilgrastim and granulocyte-macrophage colony stimulating factors)	35 (51.5%)	18 (26.9%)
Erythropoietic stimulants (Includes darbepoetin alfa, epoetin beta, folic acid, epoetin alfa, erythropoietin, Ferro-Folsan, and Hierroquick)	7 (10.3%)	12 (17.9%)
RBC Transfusions	19 (27.9%)	19 (28.4%)
Platelet Transfusions	5 (7.4%)	3 (4.5%)
Source: PIX301 CSR Table 14.3.5 and 14.3.6		

In summary, the increased rates of grade 3/4 neutropenia and leukopenia in the pixantrone group were adequately managed with growth factor support, as demonstrated by the 7% incidence of neutropenic fever and no increase in incidence of severe infections. The higher rates of infection in the pixantrone group may be associated with the higher median number of cycles of study treatment received (4 vs 3). More patients in the comparator group experienced severe anemia and required erythropoietic stimulants.

4.4 120-Day Safety Update (25 June 2009) Conclusions

Serious adverse events and cardiac safety in PIX301 continue to be monitored. Additional safety data from the ongoing PIX301 follow-up period and from three investigator-sponsored trials (IST) of pixantrone (1 ongoing with 3 patients enrolled [IST 20043] and 2 that were closed with 3 patients enrolled [IST PIX001 and IST PIX200701]) added no new information that would change the safety profile or indicate any new concerns compared to the safety data submitted in the NDA.

The data cutoff for SAE reports in patients during the follow-up period of PIX301 was 30 September 2009. These SAEs were events reported to pharmacovigilance that occurred more than 30 days after the last study treatment and were not otherwise included in the clinical study data submitted in the NDA. One patient (#087 in the pixantrone group) experienced two SAEs (MedDRA terms myelodysplastic syndrome and cardiac failure

congestive) during the PIX301 follow-up period. She received 6 cycles of pixantrone without a significant decrease in LVEF and finished the treatment period with an assessment of stable disease. She later progressed and received multiple additional regimens, including investigational therapies PTK-787 and MG-0103, followed by treatment with RICE, R-DHAP, and lastly bendamustine and rituximab. This patient's CHF symptoms occurred following 8 separate therapies for NHL and in the setting of a concurrent diagnosis of myelodysplastic syndrome (MDS). There has not been a previous report of MDS in patients receiving pixantrone, although MDS and secondary acute myelogenous leukemia have been observed following treatment with other anthracyclines, as well as with other treatment regimens for NHL.

Importantly, despite high lifetime exposure to anthracycline-like agents and pixantrone, cardiac events during follow-up were uncommon and no other nondisease-related delayed toxicities were observed. No clinically concerning changes in LVEF were observed with updated data from the PIX301 follow-up period.

4.4.1 Exposure Summary across Pixantrone Studies

In addition to PIX301,127 patients were treated with single-agent pixantrone in uncontrolled studies (most were dose-escalation). One hundred and fifty-one patients were treated with pixantrone in combination with other chemotherapies. Nearly all patients in these studies were heavily pretreated and nearly all had prior anthracycline exposure.

Number of doses and total dose are summarized in Table 25. Mean number of doses varied among the four study subgroups, consistent with the different dosing regimens of weekly x 3 every 28 days versus every 21 days.

Table 25 Extent of Exposure to Study Drug across Pixantrone Studies (Safety Population)

	Uncontrolled Single-Agent Therapy		Controlled Single-Agent Therapy (PIX301)	Combination Therapy	Total (N=348)
	NHL (N=59)	Other Malignancies (N=70)	Pixantrone Group (N=68)	All Studies (N=151)	
Number of Doses					
N	59	70	68	151	348
Mean (SD)	6.7 (5.17)	3.7 (2.64)	9.9 (5.91)	5.1 (2.61)	6.0 (4.48)
Median (range)	5.0 (1.0-18.0)	3.0 (1.0-12.0)	9.5 (1.0-18.0)	5.0 (1.0-12.0)	5.0 (1.0-18.0)
Total Dose (mg/m2)					
N	59	70	68	151	348
Mean (SD)	843.0 (821.02)	526.7 (475.94)	1459.4 (882.03)	1044.0 (553.09)	987.0 (729.09)
Median (range)	408.0 (25.5-701.2)	452.5 (29.1-2297.0)	1479.7 (100.0 - 3138)	1014.0 (155.0-2394)	786.5 (25.5-3138.0)

Source: ISS Table 5

4.4.2 Adverse Events in Other Pixantrone Studies

The pattern of AEs observed in the uncontrolled and combination study groups, which included an increased frequency of AEs coded to the System Organ Class (SOC) of Blood and Lymphatic Disorders, was consistent with that seen in Study PIX301 and the advanced cancer populations under study. There was a trend towards a higher frequency of adverse events in the combination therapy studies across multiple SOCs, which is not unexpected with multidrug regimens.

Overall, the incidence of grade 3/4 cardiac events was low across the safety population given the degree of prior cumulative exposure to anthracycline and anthracycline-like agents.

Events of cardiac failure (MedDRA terms cardiac failure and cardiac failure congestive) ≥ grade 3 occurred in 6 patients (3%) of patients receiving pixantrone as single-agent therapy and in 4 (3%) of patients receiving pixantrone in combination regimens, despite the high percentage of these patients with significant prior exposure to doxorubicin or related

compounds.

4.5 Safety Summary and Conclusions

The safety of pixantrone has been evaluated in 348 patients, which included 278 patients with NHL, nearly all of whom had extensive prior anthracycline exposure. Throughout its clinical development, the safety profile of pixantrone has demonstrated that it is well tolerated with manageable toxicities.

The primary source for the safety assessment of pixantrone was the well-controlled PIX301 trial, the first randomized controlled trial in this patient population. In that study, pixantrone, administered at a weekly dose of 85 mg/m^2 on days 1, 8 and 15 of a 28-day cycle, was well tolerated in heavily pretreated patients with relapsed or refractory aggressive NHL.

5 BENEFIT – RISK EVALUATION

Patients with relapsed or refractory aggressive NHL at or beyond second relapse have a particularly poor prognosis. There is no currently approved therapy for this indication, nor is there a standard of care regimen (NCCN 2009). Current salvage therapy rarely results in complete response, is associated with low overall response rates and when remissions occur, they are generally of short duration. Median overall survival is less than one year. Although relapsed lymphoma is still likely to be anthracycline sensitive, drugs in this class are not routinely used as patients generally will have already received close to the lifetime maximum recommended cumulative dose. Pixantrone offers healthcare providers the ability to reintroduce an anthracycline-like drug with potent antitumor effectiveness without the dose-dependent and life-threatening cardiotoxicity that would be associated with retreatment with currently available anthracycline-related drugs.

Our clinical development program included the only prospective, multicenter randomized study ever conducted in patients with relapsed or refractory aggressive NHL beyond second relapse. The PIX301 study is the first to demonstrate in a sufficiently large number of patients, and with the rigor of central independent review, that pixantrone induces previously unachievable rates of durable complete remissions and a superior clinical benefit as measured by higher CR/CRu, ORR, and PFS rates.

CR/CRu is a reasonable surrogate for clinical benefit and was shown in the present study to

predict durable responses and a major improvement in PFS, critical goals in the palliative treatment of patients with relapsed or refractory aggressive NHL. For patients enrolled in PIX301, potentially curative therapy was no longer an option. In addition to CHOP-like regimens, patients in this trial had previously been exposed to, and failed, a broad variety of standard salvage combination therapies. Therefore, allowing the investigator to choose the comparator agent for each patient was essential to avoid treating control patients with drugs which they had recently failed and to allow the choice of an agent most likely to achieve benefit based on prior therapy.

The primary endpoint of CR/CRu rate superiority was achieved (20.0 versus 5.7%; p=0.021). Three additional patients in the pixantrone arm and one in the comparator arm entered CR/CRu without additional therapy following completion of therapy as reported in the 120-Day follow-up analysis, resulting in CR/CRu rates of 24.3% vs. 7% (p=0.005) . Complete responses were more durable (median 7 months vs 3.4 months; p=0.033) in the pixantrone group. In addition, 16% of pixantrone-treated patients had a confirmed CR versus no comparator patients (0%). There was a 44% improvement in PFS for pixantrone patients (median 5.6 versus 2.6 months; HR=0.56,p=0.002) as of the 25 June 2009 data cutoff.

Data from the 25 June 2009 data cutoff also showed a 3.3 month increase in survival for the pixantrone group relative to the control group (HR=0.82, p-value=0.35). At 12 months, 21% of patients in the pixantrone group were alive and progression free, compared to 8% in the comparator group.

Pixantrone therapy was administered on an outpatient basis, and overall, pixantrone was well tolerated. Other than neutropenia, there were few grade 3-4 adverse events. The most common grade 3/4 AEs were hematologic (neutropenia), which were generally reversible and manageable with immunostimulants when required. There was a low incidence of alopecia, nausea, vomiting, mucositis, severe infection, and febrile neutropenia. Rates of severe infection were comparable between treatment groups despite the higher incidence of grade 3-4 neutropenia in pixantrone patients. There was a decrease in neutrophil nadir counts after cycle 2, and the median relative dose intensity was 91% of planned, indicating that the dose used was appropriate.

Patients who enrolled in PIX301 were allowed to have received up to 450 mg/m^2 of doxorubicin or equivalent, which is above the recommended lifetime limit for doxorubicin

when given in conjunction with cyclophosphamide or thoracic radiation. The median prior doxorubicin-equivalent dose for patients enrolling in this study was approximately 300 mg/m^2 and was similar in the two arms. Therefore, each cycle of pixantrone was projected to increase the lifetime doxorubicin-equivalent exposure by 75 mg/m^2, (450 mg/m^2 in patients who received all 6 cycles). In fact, the median doxorubicin-equivalent cumulative dose for the 22 patients (32% of the safety population) who completed 6 cycles of pixantrone on study was 695 mg/m^2, and individual patients reached lifetime dose levels of >700 mg/m^2. At these lifetime exposure levels, a very high incidence of clinically significant congestive heart failure would be expected if pixantrone possessed the cardiotoxic potential of other anthracyclines or anthracenediones.

Given the known risk for cumulative dose-related cardiac toxicity associated with anthracycline-like agents, cardiac disorders were monitored carefully throughout the trial in order to capture all cardiac events irrespective of causality. Events were also retrospectively reviewed by an independent cardiologist. Four patients in the pixantrone group and one patient in the comparator group had ≥ grade 3 cardiac adverse events during treatment, and one additional patient in the pixantrone group and one in the comparator group were reported to have developed ≥ grade 3 cardiac events in follow-up. There was no correlation between occurrence of CHF and cumulative anthracycline exposure.

As a surrogate for potential deleterious effects on cardiac function, serial cardiac MUGA scans were also performed to measure LVEF. More asymptomatic declines occurred in the pixantrone group, but only one was grade 3. There was no evidence for cumulative dose-related decline in LVEF as has been reported for doxorubicin[40] Other than one patient who developed CHF while receiving high-dose chemotherapy 12 months after treatment with 6 cycles of pixantrone, no late ≥ grade 3 CHF was observed during the additional follow-up period.

In the overall safety database (N=348), cardiac failure (MedDRA terms cardiac failure and cardiac failure congestive) events ≥ grade 3 occurred in 6 of 197 patients (3%) receiving pixantrone as single-agent therapy and in 4 of 151 patients (3%) receiving pixantrone in combination regimens.

In summary, pixantrone represents the first significant advance for the treatment of patients with relapsed or refractory aggressive NHL who have received at least two prior lines of

therapy, a patient population in need of an effective therapeutic option. The PIX301 study has shown that monotherapy with pixantrone is both effective and well tolerated in this patient population.

6 APPENDICES

APPENDIX 1 SCHEDULE OF ASSESSMENTS IN PIX301 STUDY

PIX301 Study Schedule Prestudy and During Treatment Period

	Prestudy		Cycle 1				Cycles 2 & 4				Cycles 3, 5 & 6				EOT
Cycle Day	-28 to 0		1	8	15	22	1	8	15	22	1	8	15	22	
Consent, Medical History	X														
BM Aspirate and Biopsy[1]	X														
Diagnosis/ staging	X														
Tumor assessment[2]	X						X								X
Clinical symptoms & vital signs	X		X	X	X		X	X	X		X	X	X		X
Weight , ECOG PS	X		X				X				X				X
Baseline IPI, UA, pregnancy test[3]	X														
Hematology	X		X	X	X		X	X	X		X	X	X		X
Chemistry	X		X				X				X				X
LVEF (MUGA scan)[4]	X						X						X		X
Echocardiography	X									X					X
Serum troponin T[5]	X									X					X
Concurrent disease and concomitant medications			X				X				X				X
ECG[5]	X		X				X								X
Adverse events			X	X	X		X	X	X	X	X	X	X		X
Plasma PK Analysis[6]			X				X								
Survival															X
Pixantrone administration			X	X	X		X	X	X		X	X	X		

RANDOMIZATION

[1] BM aspirate/biopsy repeated to confirm a CR or as clinically indicated.
[2] Response to be evaluated on days 50 and 106, ± 7 days.
[3] Pregnancy test for women of childbearing potential only.
[4] LVEF (by echocardiography or MUGA) and serum cardiac troponin T every 2 cycles (± 1 week) following first study treatment. If the LVEF declined by >15 percentage points (absolute decrease, e.g., 75% - 59%) from baseline on echocardiography, a MUGA was to be obtained. If a ≥ 10 percentage points decline was then found by MUGA, echocardiography or MUGA was to be performed monthly thereafter. Discontinuation decisions for decreased LVEF were to be based on MUGA results
[5] ECG to be performed after infusion on day 1 of cycles 1 and 2
[6] PK analysis was done during cycles 1 and 2 only.

The schedule of follow-up assessments for PIX301 is shown in the following table. During follow-up, efficacy assessments were performed every 2 months, and information about subsequent therapies was also collected and summarized.

PIX301 Schedule of Assessments for the Follow-Up Period										
Months since End of Treatment	1	2	4	6	8	10	12	14	16	18
LVEF (MUGA scan)				X						
Serum cardiac troponin T				X						
Adverse events [1]	X									
Tumor assessment and objective response		X	X	X	X	X	X	X	X	X
Clinical signs and symptoms/ subsequent chemotherapy		X	X	X	X	X	X	X	X	X
LDH		X	X	X	X	X	X	X	X	X
Bone Marrow Aspirate and Biopsy[2]										
Survival		X	X	X	X	X	X	X	X	X

Note: The end-of-treatment visit was to occur approximately 30 days after last dose completed.

1 All study drug-related AEs that were ongoing at the end-of-treatment visit were to be followed for the earlier of 30 days or until the patient began a non-protocol-directed treatment for NHL. Toxicity assessments also included clinically relevant laboratory abnormalities. Drug related SAEs were to be reported and followed during the follow-up period.

2 Repeat only if clinically indicated.

APPENDIX 2 INDEPENDENT ASSESSMENT PANEL (IAP) CRITERIA FOR EVALUATION OF RESPONSE (ADAPTED FROM CHESON, ET AL. 1999)

Measurable Disease

Defined as lymph node masses, liver nodules, spleen nodules, other extranodal sites of lymphoma, and lung lesions when they arise, that are greater than 1 cm in 2 perpendicular dimensions (short axis and longest transverse dimension, Fig. 1), and are clearly measurable in both dimensions.

Lymph nodes ≤1 .0 cm in 2 perpendicular dimensions are considered normal.

Bone lesions, effusions, and mucosal lesions in the gastrointestinal tract are not considered to be measurable.

Dominant (Target) Lymph Node Masses

Up to 6 measurable lymph node masses may be chosen as dominant lymph node masses. Dominant sites of disease must be lymph node masses that are >1.5 cm in 2 perpendicular dimensions, and are clearly measurable in both dimensions. The dominant lymph node masses should be chosen such that they include the largest lymph node masses and are representative of the subject's disease. If there are measurable lymph node masses in the mediastinum or retroperitoneum, at least one lymph node mass from each of those locations should always be included as dominant lymph node masses. In addition, the dominant lymph node masses should be chosen from as disparate regions of the body as possible.

Non-Dominant (Non-Target) Measurable Disease

All measurable sites of disease that are not included as dominant lymph node masses are considered non-dominant (Non-Target), measurable disease.

All other sites of disease will be considered assessable, even if they are > 1 cm in two perpendicular dimensions.

Technical Limitations for Measurements

Minimal lesion size for quantitative measurement is equal to 5 mm slice thickness.

Lesions that are visible but are too small to measure will be recorded as 0.5 X 0.5, along with a comment that they are "too small to measure." Lesions that are no longer visible will be recorded as 0.0 X 0.0, along with a comment stating they are "resolved/gone".

Disease Response Assessment

Response	Description
Complete Response (CR)	Extranodal sites of disease disappear Lesions that were >1.5 cm in both dimensions and regress to ≤1 .5 cm in both dimensions. Lesion masses that were 1.1-1.5 cm in both dimensions, and thought to contain NHL regress to ≤1 .0 cm in both dimensions or the SPD of each lymph node mass decreases by more than 75%. Resolution of splenomegly.
Complete Response/ Unconfirmed (CRu)	Liver/Spleen nodules disappear Dominant lesions SPD decreases by more than 75%. Resolution of splenomegly
Partial Response (PR)	≥50% decrease in SPD of dominant lesions, extranodal sites of disease, splenic and hepatic nodules. No increase in the size of any lesion. No new sites of disease
Stable Disease (SD)	Disease response is less than the required for PR, but the criteria for relapse or progressive disease are not met
Progressive Disease or Relapsed Disease (RD) (i.e. relapse from CR or CRu)	Appearance of any new lesion that is at least 1.5 cm in size or there is a >50% increase of the new lesion at a subsequent time point >50% increase in the SPD of previously involved sites. >50% increase in the longest diameter of any previously identified node greater than 1 cm in its short axis, >50% increase in the SPD of any one node

APPENDIX 3 DOSE MODIFICATION GUIDELINES FOR STUDY PIX301

Pixantrone Dose Modifications for Hematologic Toxicity at Cycle Days 8 and 15

If ANC was < 0.5 x 10^9/L or platelet count < 25 x 10^9/L at the assessment before treatment on day 8 or day 15, the administration on that day was to be skipped. If there was bone marrow involvement and the ANC was ≤ 0.5 x 10^9/L or the platelet count was < 10 x 10^9/L, the administration on that day was to be skipped.

Pixantrone Dose Modifications for Hematologic Toxicity	
Neutrophil Count	Dose/Schedule
≥ 1.0 x 10^9/L (if bone marrow involvement ≥ 0.5 x 10^9/L is acceptable)	No change.
≥ 0.1 x 10^9/L < 1.0 x 10^9/L, no fever	No change, delay treatment until recovery to ≥ 1.0 x 10^9/L.[1,2,3,4]
< 0.1 x 10^9/L **or** febrile neutropenia grade 3 **or** grade 4 neutropenia persisting more than 7 days	Delay treatment until recovery to > 1.0 x 10^9/L. Reduce BBR 2778 by 20%
Platelet Count	Dose/Schedule
≥ 50 x 10^9/L (if bone marrow involvement ≥ 10 x 10^9/L is acceptable)	No change.
≥ 20 x 10^9/L to < 50 x 10^9/L, no bleeding (if bone marrow involvement < 10 x 10^9/L, no bleeding)	Delay treatment until recovery (≥ 50 x 10^9/L or ≥ 10 x 10^9/L if BM involvement).
< 20 x 10^9/L or bleeding	Delay treatment until recovery (≥ 50 x 10^9/L).[4] Reduce BBR 2778 by 20%.

[1] Reduce the dose of BBR 2778 by 20% if recovery did not occur before cycle day 42.
[2] Proceed with next dose of study drug if ANC values were between 0.5 x 10^9/L and 1.5 x 10^9/L at entry *because of bone marrow infiltration by lymphoma (re inclusion criteria) and the ANC returned to baseline* (± 10%) and was above 0.5 x 10^9/L.
3. [3] G-CSF or GM-CSF and erythropoietin were to be prescribed according to the investigator's clinical judgment.
[4] G-CSF or GM-CSF was to be discontinued 24 hours prior to study drug administration.
4. If no recovery after 7 weeks from the start of the cycle, patient was to be withdrawn from the study.

Pixantrone Dose Modifications for Nonhematologic Toxicities

Nonhematologic toxicities were to be recovered to baseline or grade 1 by the beginning of the next cycle, (cycle day 29 from the previous cycle or cycle day 1 of the next cycle) in order to administer the next cycle of BBR 2778. Otherwise, the dose/schedule was to be modified according to the following table:

Pixantrone Dose Modifications for Nonhematologic Toxicity	
Toxicity Grade	Dose/Schedule
0 – 1	No change.
2	Discontinue/delay treatment until recovery to grade 1.* Retreat at the same dose level. Reduce dose by 20%, if a delay occurs for the same toxicity on any 2 occasions.
3 – 4	Discontinue/delay treatment until recovery to grade 1.* Reduce dose by 20%. Recurrence of grade 3 or 4 toxicity at the reduced dose requires patient withdrawal from the study.
* If no recovery by cycle day 49, patient was to be withdrawn from study.	

Dose Modifications for Comparator Group

Dose reduction due to toxicities should be done according to the package insert, except for oxaliplatin, which was to be modified as described in section 6.2.1 of the protocol. All precautions specified in the package insert were to be followed.

Dose Management for Cardiotoxicity

Patients were to be withdrawn from the study if they had cardiac toxicity that was NYHA functional assessment Class III or greater.

Treatment was to be discontinued for patients with an absolute decrease in LVEF from baseline values ≥20% (eg, 80% to 60%) or with an absolute LVEF level ≤40%, and clinical signs or symptoms of congestive heart failure.

Patients with an absolute decrease in LVEF from baseline values ≥ 20% (eg, 80% to 60%) or with an absolute LVEF level ≤ 40% and no clinical signs or symptoms of congestive heart failure were to have treatment held and the LVEF confirmed with a MUGA scan within 2 weeks. MUGA was to be the method of choice unless there was a clinically justifiable reason to use an ECHO. If the LVEF decrease was confirmed, the patient was to be discontinued. If the LVEF decrease was not confirmed, the clinical case was to be discussed with the medical monitor before continuing the patient in the study.

APPENDIX 4 CLINICAL STUDIES WITH PIXANTRONE IN COMBINATION REGIMENS

Clinical Studies with Pixantrone in Combination Regimens			
Study #	**Population**	**Design/Dose Regimen**	**Treated Patients (Pixantrone/ Control)**
AZA I-05	Relapsed/ Refractory Aggressive NHL	Multicenter dose escalation BSHAP: pixantrone 80 mg/m^2 day 1, cytarabine 2000 mg/m^2 day 5, cisplatin 25 mg/m^2 days 1-4, methylprednisolone 500 mg days 1-5 in 21-day cycles	18/0
AZA I-06	Relapsed/ Refractory Indolent NHL	Multicenter dose escalation Pixantrone 80-120 mg/m^2 day 2 with fixed doses of fludarabine, dexamethasone and rituximab in 28- day cycles	29/0
AZA I-07 (phase 1)	Relapsed/ Refractory Aggressive NHL	Dose escalation Pixantrone 80-180 mg/m^2 with cyclophosphamide 750 mg/m2 day 1, vincristine 1.4 mg/m2 day 1, and prednisone 100 mg days 1-5 in 21-day cycles	35/0
AZA I-07 (phase 2)	Relapsed/ Refractory Aggressive NHL	Open-label fixed dose Pixantrone 150 mg/m2 with cyclophosphamide 750 mg/m2 day 1, vincristine 1.4 mg/m^2 day 1, and prednisone 100 mg days 1-5 in 21-day cycles	30/0
AZA II-02	Relapsed/ Refractory Aggressive NHL	Open-label Pixantrone 80 mg/m^2 with fixed doses of cytarabine, methylprednisolone and cisplatin in 21- day cycles. Patients with response or SD after 2 cycles could continue study treatment for up to 6 cycles or receive further cycles of BSHAP with rituximab as mobilization for SCT.	19/0
AZA III-02	Relapsed/ Refractory Indolent NHL	Open-label randomized Rituximab with or without pixantrone 90 mg/m^2 in 21-day cycles	20/18
PIX 203	Diffuse Large B-cell Lymphoma (1st line therapy)	Randomized CPOP-R ([pixantrone 150 mg/m^2) vs CHOP-R (6 cycles)	Closed to enrollment Jan 2008 with 124 patients; follow-up ongoing

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